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TEXTBOOK of
PEDIATRICS
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1600 John F. Kennedy Blvd.
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Philadelphia, PA 19103-2899

NELSON TEXTBOOK OF PEDIATRICS, TWENTIETH EDITION
International Edition

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International Standard Book Number: 978-1-4557-7566-8

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Printed in Canada

Last digit is the print number: 9 8 7 6 5 4 3 2 1
To the Child’s Physician and especially to those who through their expressed confidence in past editions of this book have provided the stimulus for this revision.

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This is as true in 2015 as it was in 1969.

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Abnormalities of the Cornea
Abnormalities of the Lens
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Whoever saves one life it is considered as if they saved an entire world.  
— Babylonian Talmud

The 20th edition of Nelson Textbook of Pediatrics continues in its tradition of being an essential resource for pediatricians as they diagnose and treat the infants, children, and adolescents of the 21st century. The 20th edition has been thoroughly revised, updated, and edited to keep up with the growing data accumulated from basic, clinical, and population-based research. The promise that translational medicine will improve the lives of all children is greater than ever. Knowledge of human development, behavior, and diseases from the molecular to sociologic levels is increasing at fantastic rates, leading to greater understanding of health and illness in children and substantial improvements in health quality for those who have access to healthcare. These exciting scientific advances also provide hope to effectively address prevention and treatment of new and emerging diseases threatening children and their families.

The field of pediatrics encompasses advocacy for all children throughout the world and must address societal inequalities of important resources required for normal development, as well as protection from natural and manmade disasters. Unfortunately, many children throughout the world have not benefited from the significant advances in the prevention and treatment of health-related problems, primarily because of a lack of political will and misplaced priorities. For our increasing knowledge to benefit all children and youth, medical advances and good clinical practice must always be coupled with effective advocacy.

This new edition of Nelson Textbook of Pediatrics attempts to provide the essential information that practitioners, house staff, medical students, and other care providers involved in pediatric health care throughout the world need to understand to effectively address the enormous range of biologic, psychologic, and social problems that our children and youth may face. Our goal is to be comprehensive yet concise and reader friendly, embracing both the new advances in clinical science and the time-honored art of pediatric practice.

The 20th edition is reorganized and revised from the previous edition. There are many additions of new diseases and new chapters, as well as substantial expansion or significant modification of others. In addition many more tables, photographs, imaging studies, and illustrative figures, as well as up-to-date references, have been added. Although, to an ill child and his or her family and physician, even the rarest disorder is of central importance, all health problems cannot possibly be covered with the same degree of detail in one general textbook of pediatrics. Thus, leading articles and subspecialty texts are referenced and should be consulted when more information is desired.

The outstanding value of the 20th edition of the textbook is due to its expert and authoritative contributors. We are all indebted to these dedicated authors for their hard work, knowledge, thoughtfulness, and good judgment. Our sincere appreciation also goes to Kate Dimock and Jennifer Shreiner at Elsevier and to Carolyn Redman at the Pediatric Department of the Medical College of Wisconsin. In addition, we thank Barbara Ruggeri for her excellent library science skills and for keeping us up to date with the literature. We have all worked hard to produce an edition that will be helpful to those who provide care for children and youth and to those desiring to know more about children’s health worldwide.

In this edition we have had informal assistance from many faculty and house staff of the departments of pediatrics at the Medical College of Wisconsin, Wayne State University School of Medicine, University of Pennsylvania School of Medicine, and University of Rochester School of Medicine. The help of these individuals and of the many practicing pediatricians from around the world who have taken the time to offer thoughtful feedback and suggestions is always greatly appreciated and helpful.

Last and certainly not least, we especially wish to thank our families for their patience and understanding, without which this textbook would not have been possible.

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The Field of Pediatrics

Chapter 1
Overview of Pediatrics
Bonita F. Stanton and Richard E. Behrman

Pediatrics is the only discipline dedicated to all aspects of the well-being of infants, children, and adolescents, including their health; their physical, mental, and psychologic growth and development; and their opportunity to achieve full potential as adults. Pediatricians must be concerned not only with particular organ systems and biologic processes, but also with environmental, social, and political influences, which have a major impact on the health and well-being of children and their families.

Children cannot advocate for themselves. As the professionals whose entire purpose is to advance the well-being of children, pediatricians must be advocates for the individual child and for all children, irrespective of culture, religion, gender, race, or ethnicity or of local, state, or national boundaries. The more politically, economically, or socially disenfranchised a population or a nation is, the greater the need for advocacy for children. The young are often among the most vulnerable or disadvantaged in society and thus their needs require special attention. As divides between nations blur through modern transportation, communication and economics, through global climate change, through contemporary means of warfare, and through uneven development within and across countries, a global, rather than a national, perspective for the field of pediatrics becomes both a reality and a necessity. The interrelation of health issues across the globe has achieved widespread recognition in the wake of the SARS (severe acute respiratory syndrome) and AIDS epidemics, expansions in the pandemics of cholera and West Nile virus, war and bioterrorism, the tsunami of 2004, the global recession beginning in 2008, the “Arab Spring” beginning in 2010, and the growing severity of hurricanes and cyclones.

More than a century ago, pediatrics emerged as a medical specialty in response to increasing awareness that the health problems of children differ from those of adults and that a child’s response to illness and stress varies with age. In 1959, the United Nations issued the Declaration of the Rights of the Child, articulating the universal presumption that children everywhere have fundamental needs and rights.

VITAL STATISTICS ABOUT CHILD HEALTH
(See Also Chapter 1.1)

From 1990 to 2010, the world population grew at an annual rate of 1.3% per yr, down from 1.8% annually during the prior 20 yr. The annual growth rate from 2010 to 2030 is expected to further decline to 0.9%. Worldwide, children younger than age 18 yr account for 2.2 billion (30%) of the world’s 7.02 billion persons. In 2010, there were an estimated 135 million births worldwide, 121 million (90%) of which were in developing countries. India, with 27.2 million births annually, is home to the largest number, followed by China at 16.5 million.

Despite global interconnectedness, the health problems of children and youth vary widely between and within populations in the nations of the world depending on a number of often interrelated factors. These factors include (1) economic considerations (economic disparities); (2) educational, social, and cultural considerations; (3) the prevalence and ecology of infectious agents and their hosts; (4) climate and geography; (5) agricultural resources and practices (nutritional resources); (6) stage of industrialization and urbanization; (7) the gene frequencies for some disorders; (8) the health and social welfare infrastructure available within these countries; and (9) political focus and stability. The state of health of any community is defined by the incidence of illness and by data from studies that show the changes that occur with time and in response to programs of prevention, case finding, therapy, and surveillance. To ensure that the needs of children and adults across the globe were not obscured by local needs, in 2000 the international community established 8 Millennium Development Goals (MDGs) to be achieved by 2015 (http://www.countdown2015mchn.org). Although all 8 MDGs impact child well-being, MDG 4 (“Reduce by two-thirds, between 1990 and 2015, the under-five mortality rate”) is exclusively focused on children.

Great strides have been made toward achieving the MDGs. Globally, there has been a reduction in under-5 mortality since 1990 from 90 to 48 deaths per 1,000 live births, with a reduction from 15 to 6 deaths in developed countries and from 99 to 53 deaths in developing countries. With the exception of sub-Saharan Africa and Oceania, all global regions reduced their under-5 mortality rate by more than half from 1990 to 2012. There were nearly 13 million under-5 deaths in 1990; 2006 marked the first year that there were fewer than 10 million deaths (9.7 million), which further decreased to 9.0 million in 2007, 8.8 million in 2008, 7.6 million in 2010, and 6.6 million in 2012. Despite these substantial successes, the annual rate of reduction in the global under-5 mortality rate of 3.9% remains below the MDG targeted rate of 4.4%, necessary to achieve the goal of a ½ reduction in the 1990 rate by 2015 (Fig. 1-1).

The infant mortality rate (deaths of children <1 yr) accounts for 83% of the under-5 mortality rate in industrialized countries, but only 64% of the rate in the least-developed nations. Neonatal (<1 mo) death contributes substantially to the under-5 mortality rate, growing in proportion as the under-5 death rate decreases. The neonatal mortality rate has been slower to decline. Globally, the neonatal mortality rate of 23 per 1,000 live births represents 57% of the infant mortality rate of 40 per 1,000 live births and 40% of the under-5 death rate (up from 37% in 1990). The neonatal mortality rate is responsible for 50% of the under-5 mortality rate in industrialized nations, 40% of the rate in developing countries, but only 33% in the least-developed countries. Most of the decline in infant mortality in the United States and other industrialized countries since 1970 is attributable to a decrease in the birthweight-specific infant mortality rate related to neonatal intensive care, not to the prevention of low-birthweight births (see Chapter 93).

Across the globe, there are significant variations in infant mortality rates by nation, by region, by economic status, and by level of industrial development, the categorizations employed by the World Bank and the United Nations (Table 1-1; see also Figs. 1-8 and 1-9). As of 2012 three nations in the world still have an under-5 mortality rate of ≥150 per 1,000 live births (Sierra Leone, 182; Angola, 164, Chad, 150), with an additional 13 nations having ≥100 deaths per 1,000 live births. Although these 3 nations are among the poorest in the world, many of their economic matches have enjoyed greater improvements in child survival in recent years, demonstrating that economics are important but that other factors, such as political will, are also important. Similarly in 2012, the United States, with one of the 10 highest gross national incomes in the world, had an under-5 mortality rate of 7 per 1,000 live births; 39 nations had lower under-5 mortality rates, with 9 countries having a rate of 3 and 2 countries having a rate of 2 per 1,000 live births.

Causes of under-5 mortality differ markedly between developed and developing nations. In developing countries, 66% of all deaths resulted from infectious and parasitic diseases. Among the 42 countries having
90% of childhood deaths, diarrheal disease accounted for 22% of deaths, pneumonia 21%, malaria 9%, AIDS 3%, and measles 1%. Neonatal causes contributed to 33%. The contribution for AIDS varies greatly by country, being responsible for a substantial proportion of deaths in some countries and negligible amounts in others. Likewise, there is substantial co-occurrence of infections; a child may die with HIV, malaria, measles, and pneumonia. Infectious diseases are still responsible for much of the mortality in developing countries. In the United States, pneumonia (and influenza) accounted for only 2% of under-5 deaths, with only negligible contributions from diarrhea and malaria. Unintentional injury is the most common cause of death among U.S. children ages 1-4 yr, accounting for approximately 33% of deaths, followed by congenital anomalies (11%), homicides (9%), and malignant neoplasms (8%). Other causes accounted for <5% of total mortality within this age group (Table 1-2). Although unintentional injuries in developing countries are proportionately less important causes of mortality than in developed countries, their absolute rates and their contributions to morbidity are substantially greater.

Just as economic status of a country as a whole is closely correlated with child survival, so too is relative wealth within a country. Poorer children in nations worldwide have higher death rates than their wealthier national counterparts (Fig. 1-2).

Causes of death vary by developmental status of the nation. In the United States, the 3 leading causes of death among infants were congenital anomalies, disorders related to gestation and low birthweight, and sudden infant death (see Table 1-2). By contrast, in developing countries, the majority of infant deaths are caused by infectious diseases; even in the neonatal period, 24% of deaths are caused by severe infections and 7% by tetanus. Although immunization rates remain higher in industrialized nations compared to developing nations, this gap is closing. In 2010, immunization percentage rates against diphtheria, pertussis, tetanus, measles, and polio were in the mid-90s; comparable levels in developing countries were in the mid-80s, with rates in the least-developed countries very close. In developing countries, 29% of neonatal deaths are caused by birth asphyxia and 24% are caused by complications of prematurity.

A consistently robust predictor of infant mortality across the globe is a poor level of maternal education (consequently, another of the MDGs addresses the need for universal access to schooling for girls; Fig. 1-3). Other maternal risk characteristics, such as unmarried status, adolescence, and high parity, correlate with increased risk of postneonatal mortality and morbidity and low birthweight.

Table 1-1 Child Health Indicators Worldwide by Region

<table>
<thead>
<tr>
<th>Region</th>
<th>Mortality Rate by Yr Per 1,000 Live Births</th>
<th>GROSS NATIONAL PER CAPITA INCOME</th>
<th>LIFE EXPECTANCY AT BIRTH</th>
<th>PRIMARY SCHOOL ATTENDANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-Saharan Africa</td>
<td>177 98</td>
<td>107 64</td>
<td>32</td>
<td>$1,397</td>
</tr>
<tr>
<td>Eastern and Southern Africa</td>
<td>163 77</td>
<td>101 51</td>
<td>28</td>
<td>$1,729</td>
</tr>
<tr>
<td>West and Central Africa</td>
<td>195 118</td>
<td>115 76</td>
<td>37</td>
<td>$1,071</td>
</tr>
<tr>
<td>Middle East and North Africa</td>
<td>71 30</td>
<td>53 24</td>
<td>15</td>
<td>—</td>
</tr>
<tr>
<td>South Asia</td>
<td>129 60</td>
<td>92 47</td>
<td>32</td>
<td>$1,440</td>
</tr>
<tr>
<td>East Asia and Pacific</td>
<td>58 20</td>
<td>44 17</td>
<td>11</td>
<td>$5,592</td>
</tr>
<tr>
<td>Latin America and Caribbean</td>
<td>54 19</td>
<td>43 16</td>
<td>10</td>
<td>$9,212</td>
</tr>
<tr>
<td>CEE/CIS</td>
<td>47 19</td>
<td>38 16</td>
<td>9</td>
<td>$8,727</td>
</tr>
<tr>
<td>Least-developed countries</td>
<td>172 85</td>
<td>107 58</td>
<td>30</td>
<td>$779</td>
</tr>
<tr>
<td>World</td>
<td>90 48</td>
<td>63 35</td>
<td>21</td>
<td>$10,132</td>
</tr>
</tbody>
</table>

CEE/CIS, Central and Eastern Europe/Commonwealth of Independent States (formerly the USSR).
Adapted from UNICEF: The state of the world’s children 2014: Statistical Table, New York, 2012, UNICEF, Table 1, p. 35.
Table 1-2 Leading Causes of Death and Numbers of Deaths, According to Age: United States, 2010

<table>
<thead>
<tr>
<th>AGE AND RANK ORDER</th>
<th>CAUSE OF DEATH</th>
<th>NUMBER</th>
<th>PERCENT OF TOTAL DEATHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 1 yr</td>
<td>All causes</td>
<td>24,586</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Congenital malformations, deformations, and chromosomal abnormalities</td>
<td>5,107</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>Disorders related to short gestation and low birthweight, not elsewhere classified</td>
<td>4,148</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>Sudden infant death syndrome</td>
<td>2,063</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>Newborn affected by maternal complications of pregnancy</td>
<td>1,561</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>Unintentional injuries</td>
<td>1,110</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Newborn affected by complications of placenta, cord, and membranes</td>
<td>1,030</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Bacterial sepsis of newborn</td>
<td>583</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Respiratory distress of newborn</td>
<td>514</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Diseases of the circulatory system</td>
<td>507</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Newborn affected by maternal complications of pregnancy</td>
<td>472</td>
<td>2%</td>
</tr>
<tr>
<td>1-4 yr</td>
<td>All causes</td>
<td>4,316</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Unintentional injuries</td>
<td>1,394</td>
<td>32%</td>
</tr>
<tr>
<td></td>
<td>Congenital malformations, deformations, and chromosomal abnormalities</td>
<td>507</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td>Homicide</td>
<td>385</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>Malignant neoplasms</td>
<td>346</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>Diseases of heart</td>
<td>159</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Influenza and pneumonia</td>
<td>91</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Septicemia</td>
<td>62</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>In situ neoplasms, benign neoplasms, and neoplasms of uncertain or unknown behavior</td>
<td>59</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Certain conditions originating in the perinatal period</td>
<td>52</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Chronic lower respiratory diseases</td>
<td>51</td>
<td>1%</td>
</tr>
<tr>
<td>5-14 yr</td>
<td>All causes</td>
<td>5,279</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Unintentional injuries</td>
<td>1,643</td>
<td>31%</td>
</tr>
<tr>
<td></td>
<td>Malignant neoplasms</td>
<td>916</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>Congenital malformations, deformations, and chromosomal abnormalities</td>
<td>298</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>Suicide</td>
<td>274</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Homicide</td>
<td>261</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Diseases of heart</td>
<td>185</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Chronic lower respiratory diseases</td>
<td>133</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular diseases</td>
<td>90</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>In situ neoplasms, benign neoplasms, and neoplasms of uncertain or unknown behavior</td>
<td>82</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Influenza and pneumonia</td>
<td>71</td>
<td>1%</td>
</tr>
<tr>
<td>15-24 yr</td>
<td>All causes</td>
<td>29,551</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Unintentional injuries</td>
<td>12,341</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>Homicide</td>
<td>4,678</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td>Suicide</td>
<td>4,600</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td>Malignant neoplasms</td>
<td>1,604</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Diseases of heart</td>
<td>1,028</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Congenital malformations, deformations, and chromosomal abnormalities</td>
<td>412</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular diseases</td>
<td>190</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td>Influenza and pneumonia</td>
<td>181</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
<td>165</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td>Pregnancy, childbirth, and the puerperium</td>
<td>163</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Adapted from National Center for Health Statistics: Health, United States, 2013: with special feature on prescription drugs. Hyattsville, MD, 2014, Department of Health and Human Services, Table 23, p. 98.

The Changing Pediatric World

A profound improvement in child health within industrialized nations occurred in the 20th century with the introduction of antibacterial disinfectants, antibiotic agents, and vaccines. Efforts to control infectious diseases were complemented by better understanding of nutrition. In the United States, Canada, and parts of Europe, new and continuing discoveries in these areas led to establishment of public well-child clinics for low-income families. Although the timing of control of infectious disease was uneven around the globe, this focus on control was accompanied by significant decreases in morbidity and mortality in all countries. The smallpox eradication program of the 1970s resulted in the global eradication of smallpox in 1977. The introduction in the 1970s of the Expanded Program of Immunizations (universal vaccination against polio, diphtheria, measles, tuberculosis, tetanus, and pertussis) by the World Health Organization (WHO) and United Nations Children’s Fund (UNICEF) has resulted in an estimated annual reduction of 1-2 million deaths per year globally. Recognizing the importance of prevention of infectious diseases to the health of children, several countries among the 50 ranked by the World Bank as among the poorest nations (per capita income <$750/yr) have invested heavily in infectious disease control through the development of internal vaccine production capability. From 2000 to 2010, globally there was a 74% decline (with sub-Saharan Africa witnessing an 85% decline) in deaths caused by measles as a result of increased vaccination. As diarrheal diseases continued through the mid-1970s to account for ~25% of infant and childhood deaths in developing countries (~4 million deaths per year at that time), attention turned to the development and utilization of oral resuscitation fluids to sustain children through potentially life-threatening episodes of acute diarrheal diseases. Oral rehydration solutions are largely credited with the current reduction of diarrheal deaths annually to 1.5 million. Substantial improvements have been witnessed in malaria control (global decrease of incidence by 17% and mortality rate by 25% since 2000). There have been substantial increases in the percent of households having insecticide-treated bed nets and improvement of children with fever in endemic areas receiving antimalarial drugs.

In the later 20th century, with improved control of infectious diseases (including the elimination of polio in the Western hemisphere)
through both prevention and treatment, pediatric medicine in industrialized nations increasingly turned its attention to a broad spectrum of conditions. These included both potentially lethal conditions and temporarily or permanently handicapping conditions; among these disorders were leukemia, cystic fibrosis, diseases of the newborn infant, congenital heart disease, mental retardation, genetic defects, rheumatic diseases, renal diseases, and metabolic and endocrine disorders.

Increasing attention has also been given to behavioral and social aspects of child health, ranging from reexamination of child-rearing practices to creation of major programs aimed at prevention and management of abuse and neglect of infants and children. Developmental psychologists, child psychiatrists, neuroscientists, sociologists, anthropologists, ethnologists, and others have brought us new insights into human potential, including new views of the importance of the environmental circumstances during pregnancy, surrounding birth, and in the early years of child rearing. The later 20th century witnessed the beginning of nearly universal acceptance by pediatric professional societies of attention to normal development, child rearing, and psychosocial disorders across the continents. In the past decade, irrespective of level of industrialization, nations have developed programs addressing not only causes of mortality and physical morbidity (such as infectious diseases and protein-calorie malnutrition), but also factors leading to decreased cognition and thwarted psychosocial development, including punitive child-rearing practices (whether at home or in school) and wife abuse, child labor, undernutrition, war, and poor-quality schooling. Obesity is recognized as a major health risk not only in industrialized nations, but increasingly in transitional countries. Progress at the turn of the 21st century in unraveling the human genome offers for the first time the realization that significant genetic screening, individualized pharmacotherapy, and genetic manipulation will be a part of routine pediatric treatment and prevention practices in the future. The prevention implications of the genome project give rise to the possibility of reducing costs for the care of illness but also increase concerns about privacy issues (see Chapter 3).

Although local famines and disasters, and regional and national wars have periodically disrupted the general trend for global improvement in child health indices, it was not until the advent of the AIDS epidemic in the later 20th century that the first substantial global erosion of progress in child health outcomes occurred. This erosion resulted in ever-widening gaps between childhood health indices in sub-Saharan Africa compared to the rest of the world. From 1990 to 2002, life expectancy in sub-Saharan Africa decreased from 50 yr to 46 yr. However, as of 2008, it had returned to 52 yr and in 2012 was 56 yr. Wide distribution of effective antiretroviral therapy (Fig. 1-4), aggressive HIV prevention education, and increased access to antitubercular drugs have been important in these successes, but continued success will require sustained international support. Despite this positive news, children with HIV remain the least-likely group to receive antiretroviral treatment. Despite these gains, diseases once confined to limited geographic niches, including West Nile virus, and diseases previously uncommon among humans, such as the avian flu virus, increased awareness of the interconnectedness of health around the world and the impact of global warming. Formerly perceived as a problem of industrialized nations, motor vehicle crashes are now recognized as a major cause of mortality in developing countries.

### MORBIDITIES AMONG CHILDREN

Adequately addressing special healthcare needs is important in all countries, both to minimize loss of life and to maximize the potential of each individual.

In the United States, $\approx$70% of all pediatric hospital bed days are for chronic illnesses; 80% of pediatric health expenditures are for 20% of children. Approximately 14% of U.S. children have special healthcare needs, ranging from 10% to 19.8% across the 50 states and the District of Columbia. One in 5 households with children had $\geq$1 children with special healthcare needs (see Chapter 42). Significantly, more poor children and minority children have special healthcare needs.

Although there are numerous chronic conditions and the prevalence of these disorders vary by population, 2 of these morbidities—asthma...
Chronic cognitive morbidities represent another substantial problem. Although different diagnostic criteria have been applied, attention-deficit/hyperactivity disorder has been identified in 5–12% of children in countries across the globe, with a worldwide estimated prevalence of 5.29%. Rates exceeding 10% have been reported in the United States, New Zealand, Australia, Spain, Italy, Colombia, and Great Britain. Variations in cultural tolerance and/or differences in screening approaches or tools may account for some of the differences in prevalence of the disorder by country, but genetic and gene–environmental interactions may also play a role. Despite variations in rate, the condition is universal. Beyond the personal and familial stress caused by the disorder, costs to the educational systems are considerable. In countries where they are available, drug costs are considerable; in the United States, annual costs for drug treatments for attention-deficit/hyperactivity disorder are estimated to exceed $4 billion. In developing countries without resources for special education, these children are unlikely to fulfill their academic potential (see Chapter 33).

Mental retardation affects ∼1–3% of children in the United States, with ∼80% of these children having mild retardation. Rates are several fold higher among very-low birthweight infants. In the United States, there is substantial variation in rates of mild retardation by socioeconomic status (9-fold higher in the lowest compared to the highest socioeconomic stratum), but relatively equivalent rates of severe retardation. A similar income-related distribution is found in other countries, including some of the most impoverished countries, such as Bangladesh. Lower overall rates have been reported in some countries, including countries ranging from Saudi Arabia to Sweden to China; the difference is primarily in the prevalence of mild retardation (see Chapter 36).

Posttraumatic stress disorder (PTSD) in children remains underrecognized. PTSD can follow violent attacks and witnessed violence, sexual abuse, natural disasters, motor vehicle accidents, kidnapping, and domestic violence. Female gender, prior exposure to violence, other psychologic disturbances, and low social support are also associated with its appearance after an exposure. The prevalence of childhood PTSD varies considerably around the globe, but in children with substantial exposure to violence, the rates appear to be very high. After the attacks on the World Trade Center towers and the Pentagon in 2001, 33% of U.S. children had experienced 1 or more symptoms of PTSD. The prevalence of PTSD among children and adolescents exposed to the tsunami of 2004 were 57%, 46%, 31%, 10%, and 7% 6 wk, 6 mo, 1 year, 18 mo, and 2 yr post exposure, respectively. Children hit by the waves had significantly higher rates of PTSD.

SITUATIONAL SPECIAL-RISK POPULATIONS

Children at situational special risk have had their futures compromised by actions or policies arising from their families, schools, communities, nations, or the international community. These problems have several causes, whether the end result is homeless children, runaway children, children in foster care, or children in other disadvantaged groups.

Children in Urban Settings

Over half of the world’s population is urban dwellers. Although urban settings historically have offered educational, medical, recreational, and employment opportunities, an increasing number of urban dwellers are living in marginal communities with a growing gap in access to clean water, adequate sanitation or dependable electricity as the urban population rapidly increases (Fig. 1-5). As has been seen in Port-au-Prince, Haiti, after the devastating earthquake of 2010, national disasters exact an especially high toll on children and families living in makeshift homes on lands that are not intended for housing.

Children in Poverty

Family income is central to the health and well-being of children. Children living in poor families, especially those located in poor communities, are much more likely than children living in upper- or middle-class families to experience material deprivation and poor health, die during childhood, score lower on standardized tests, be
restrained in a grade or drop out of school, have out-of-wedlock births, experience violent crime, end up as poor adults, and suffer other undesirable outcomes. As of 2010, worldwide, 22% of the population lives below the international poverty line of U.S. $1.25 per capita per day; 47% of sub-Saharan and 50% of the least-developed nations live below this amount. Poverty rates are higher for children than adults and are highest for infants and toddlers. Higher in general in developing countries, within each country, the rate of infant mortality among the poorest quintile of the population is about twice that of the wealthiest quintile (see Fig. 1-2).

In the United States, from 1990 to 2000, the percentage of children <18 yr living below the poverty line had decreased from 21% to 16%. In 2010, 2 yr after the start of the recession, the rate had risen to 22%. Black and Hispanic children consistently have had higher poverty rates than Asian and white children. In 2010, 39% of black children and 35% of Hispanic children lived in poverty, compared to 14% of Asian children and 12% of white children. Sixty-six percent of black and Hispanic children compared to only 33% of Asian and 29% of white children lived below 200% of the poverty level. Children who are poor have higher-than-average rates of death and illness from almost all causes (exceptions being suicide and motor vehicle crashes, which are most common among white, nonpoor children). Many factors associated with poverty are responsible for these illnesses: crowding, poor hygiene and healthcare, poor diet, environmental pollution, poor education, and stress.

Poverty and economic loss diminish the capacity of parents to be supportive, consistent, and involved with their children. Clinicians at all times, but especially in the context of a national or global recession, need to be especially alert to the development and behavior of children whose parents have lost their jobs or who live in permanent poverty. Fathers who become unemployed frequently develop psychosomatic symptoms, and their children often develop similar symptoms. Young children who grew up in the Great Depression in the United States and whose parents were subject to acute poverty suffered more than older children, especially if the older ones were able to take on responsibilities for helping the family economically. Such responsibilities during adolescence seem to give purpose and direction to an adolescent's life. The younger children, faced with parental depression and unable to do anything to help, suffered a higher frequency of illness and a diminished capacity to lead productive lives even as adults.

The pediatric team should ask parents about their economic resources, adverse changes in their financial situation, and the family's attempts to cope. Encouraging concrete methods of coping, suggesting ways to reduce stressful social circumstances while increasing social networks that are supportive, and referring patients and their families to appropriate welfare, job training, and family agencies can significantly improve the health and functioning of children at risk when their families live in poverty. In many cases, special services, especially social services, need to be added to the traditional medical services; outreach is required to find and encourage parents to use health services and bring their children into the healthcare system. Pediatricians also have the responsibility to contribute to, and advocate for, safety net services for impoverished children within and outside the boundaries of their own country. An increasing number of programs are available to help children of greatest need worldwide, such as Project Smile, CARE, Project Hope, and Doctors Without Borders.

Children of Immigrants and Racial Minority Groups Including U.S. Native Americans

Immigrants comprise >15% of the population in >50 countries, including many Western European countries. Thirteen percent of the U.S. population is foreign-born; 24% of all children in the United States <17 yrs have immigrant parents. The United States is experiencing a wave of immigration larger than that occurring in the early 20th century. Until the mid-20th century, emigrants to the United States were primarily white and from Europe. Such individuals now represent only approximately 10% of immigrants; the remainder are overwhelmingly of color and from throughout the world, including 29% from Mexico, 5% from China, and 4% each from India and the Philippines. Although immigrants in the United States have faced discrimination and oppression throughout history, the potential for such discrimination is compounded by the racial differences represented in the current immigrant pool. In the United States, about 240,000 children legally immigrate each year, and, through 2010, an estimated 50,000/yr entered the country illegally. In recent years the number of children from Latin American countries entering illegally has greatly increased, with estimates of more than 90,000 such children entering in 2014 alone. An estimated 5.5 million children have at least 1 illegal immigrant parent; this number doubled from 2000 to 2010.

The immigrant population constitutes a substantial proportion of the low-wage labor market. Immigrants represent 16% of all U.S. workers but 20% of low-wage workers. Immigrants are twice as likely as U.S.-born citizens to earn less than minimum wage. The poverty rate of children in immigrant families is 50% greater than in U.S.-born families; over the past decade children with 2 immigrant parents consistently have a 15% greater likelihood of living below the poverty line than children in nondocumented families. Contributing to the lack of access to higher-salaried jobs is the lack of proficiency in English (>52% of immigrants) and the lack of education (40% have not completed high school). Immigrants account for 29% of the uninsured in the United States.

Families of different origins obviously bring different health problems and different cultural backgrounds, which influence health practices and use of medical care. To provide appropriate services, clinicians need to understand these influences (see Chapter 4). The high prevalence of hepatitis among women from Southeast Asia makes use of hepatitis B vaccine essential for their newborns. Children from Southeast Asia and South America have growth patterns that are generally below the norms established for children of Western European origin, as well as high rates of hepatitis, parasitic diseases, and nutritional deficiencies and high degrees of psychosocial stress. Foreign-born children may surpass American-born children in some health outcomes, but their health deteriorates as they become acculturated (see Chapter 4).

Refugee children who escape from war or political violence and whose families have been subjected to extreme stress represent a subset of immigrant children who have faced severe trauma. These children have a particularly high incidence of mental and behavioral problems (see Chapter 39). Armed conflicts in 2011 resulted in an especially high (4 million) number of refugees worldwide.

Linguistically isolated households, in which no one older than 14 yr of age speaks English, often present significant obstacles to providing quality healthcare to children because of difficulties in understanding and communicating basic concerns and instructions, avoiding...
compromising privacy and confidentiality interests, and obtaining informed consent (see Chapter 4).

The United States is home to multiple minority populations, including the 2 largest groups, Latinos and African-Americans. The nonwhite minority groups will constitute >50% of the U.S. population by 2050. Nonwhite children in the United States disproportionately experience adverse child health outcomes (Tables 1-3 and 1-4). Infants that are born to African-American mothers experience low birthweight and infant mortality rates twice those with white mothers (see Chapter 93). Rates of these 2 adverse health outcomes are also substantially higher among some groups of Hispanic infants and children, the rates are particularly high among those of Puerto Rican descent (>1.5 times the rates for white infants). In 2010, the overall infant mortality rate was 6.4 per 1,000 live births, whereas that for non-Hispanic African-American infants was 11.7; for Native Americans, 8.3; and Puerto Ricans, 7.1. Mexicans, Asians, Pacific Islanders, Central and South Americans, and Cubans were below the national average. Latino, Native American, and African-American children are substantially more likely to live in poverty than are white children.

There are approximately 5.1 million Native Americans (including those with mixed races/ethnicities) and 566 federally recognized tribes. The Native American population increased by 26% from 2000 to 2010 compared to a national increase of only 9.7%. Approximately 60% of Native Americans live in urban areas, not on or near native lands. Like their minority immigrant counterparts, they have faced social and economic discrimination. The unemployment and poverty levels of Native Americans are, respectively, 3-fold and 4-fold that of the white population, and far fewer Native Americans graduate from high school or go to college. The rate of low birthweight among Native Americans is more than the white rate but less than the black rate. The neonatal and the postneonatal mortality rates are higher for Native Americans living in urban areas than for urban white Americans. Deaths in the first year of life from sudden infant death syndrome, pneumonia, and influenza are higher than the average in the United States, whereas deaths as a result of congenital anomalies, respiratory distress syndrome, and disorders relating to short gestation and low birthweight are similar.

Unintended injury deaths among Native Americans occur at twice the rate for other U.S. populations; deaths caused by malignant

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**Table 1-3** Deaths Rates for All Causes Among Children and Young Adults According to Sex, Race, Hispanic Origin, and Age: 2010

<table>
<thead>
<tr>
<th></th>
<th>Deaths Per 100,000 Resident Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UNDER 1 yr</td>
</tr>
<tr>
<td>All persons</td>
<td>623.4</td>
</tr>
<tr>
<td>Male</td>
<td>680.2</td>
</tr>
<tr>
<td>Female</td>
<td>564.0</td>
</tr>
<tr>
<td><strong>MALES</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>584.3</td>
</tr>
<tr>
<td>Black male</td>
<td>1206.5</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>542.5</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>434.4</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>556.8</td>
</tr>
<tr>
<td>White not Hispanic or Latino</td>
<td>594.4</td>
</tr>
<tr>
<td><strong>FEMALES</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>575.9</td>
</tr>
<tr>
<td>Black (African-American)</td>
<td>488.0</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>366.4</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>341.8</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>462.9</td>
</tr>
<tr>
<td>White not Hispanic or Latino</td>
<td>480.4</td>
</tr>
</tbody>
</table>

Adapted from National Center for Health Statistics: Health, United States, 2013: with special feature on prescription drugs, Hyattsville, MD, 2014, Department of Health and Human Services, Tables 11, p. 98, and 17, p. 71.

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**Table 1-4** Infant, Neonatal, and Postnatal Deaths and Mortality Rates by Specified Race or Origin of Mother: United States, 2009 and 2010

<table>
<thead>
<tr>
<th>RACE OF MOTHER</th>
<th>YEAR(S)</th>
<th>INFANT</th>
<th>NEONATAL</th>
<th>POSTNATAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>All races</td>
<td>2007</td>
<td>6.4</td>
<td>4.2</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>2008</td>
<td>6.1</td>
<td>4.0</td>
<td>2.1</td>
</tr>
<tr>
<td>White</td>
<td>2007</td>
<td>5.3</td>
<td>3.5</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>2008</td>
<td>5.2</td>
<td>3.5</td>
<td>1.8</td>
</tr>
<tr>
<td>Black or African American</td>
<td>2007</td>
<td>12.1</td>
<td>8.0</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td>2008</td>
<td>11.2</td>
<td>7.3</td>
<td>3.9</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>2007</td>
<td>8.3</td>
<td>4.3</td>
<td>4.0</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>2007</td>
<td>4.3</td>
<td>3.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>2007</td>
<td>5.3</td>
<td>3.6</td>
<td>1.7</td>
</tr>
<tr>
<td>Mexican</td>
<td>2007</td>
<td>5.1</td>
<td>3.5</td>
<td>1.6</td>
</tr>
<tr>
<td>Puerto Rican</td>
<td>2007</td>
<td>7.1</td>
<td>4.8</td>
<td>2.3</td>
</tr>
<tr>
<td>Cuban</td>
<td>2007</td>
<td>3.8</td>
<td>2.9</td>
<td>2.1*</td>
</tr>
<tr>
<td>Central and South American</td>
<td>2007</td>
<td>4.4</td>
<td>3.0</td>
<td>1.4</td>
</tr>
<tr>
<td>Other and unknown</td>
<td>2007</td>
<td>6.1</td>
<td>4.0</td>
<td>2.1</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>2007</td>
<td>5.2</td>
<td>3.4</td>
<td>1.8</td>
</tr>
<tr>
<td>White</td>
<td>2007</td>
<td>11.5</td>
<td>7.5</td>
<td>4.0</td>
</tr>
<tr>
<td>Black or African American</td>
<td>2007</td>
<td>11.5</td>
<td>7.5</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Adapted from National Center for Health Statistics: Health, United States, 2013: with special feature on prescription drugs, Hyattsville, MD, 2014, Department of Health and Human Services, Tables 11, p. 98, and 17, p. 71.

*2009.*
neoplasms are lower. During adolescence and young adulthood, suicide and homicide are the second and third causes of death in this population and occur at about twice the rates of the rest of the population. There may be significant underreporting of deaths of Native American children.

As many as 75% of Native American children have recurrent otitis media and high rates of hearing loss, resulting in learning problems. Tuberculosis and gastroenteritis, formerly much more common among Native Americans, now occur at about the national average. Psychosocial problems are more prevalent in these populations than in the general population: depression, alcoholism, drug abuse, out-of-wedlock teenage pregnancy, school failure and dropout, and child abuse and neglect.

An estimated 300 million indigenous persons live in 70 countries (50% in Asia) and speak ~4,000 languages. Such children endure lower vaccination rates, lower school entry and higher dropout rates, higher rates of poverty, and lower access to justice. Indigenous children in Latin America account for 66% of the deaths of children younger than age 2 yr.

Children of Migrant Workers
Families facing economic hardship have been forced to leave their land and homes in search of better opportunities; such migrations are often within a country or between neighboring countries.

In the United States, the number of migrant and seasonal farm workers is estimated to exceed 3 million, with 68% born in Mexico; 52% are parents, often accompanied by their children as they travel from site to site. The families experience poor housing, frequent moves, and a socioeconomic system controlled by a crew boss who arranges the jobs, provides transportation, and often, together with the farm owners, provides food, alcohol, and drugs under a "company store" system that leaves migrant families with little money or in debt. Children often go without schooling. English skills are limited, with 35% speaking no English and 27% "a little." The average family income is $17,500 to $19,999. Only 8% report receiving health insurance.

The medical problems of children of migrant farm workers are similar to those of children of homeless families: increased frequency of infections (including HIV), trauma, poor nutrition, poor dental care, low immunization rates, exposures to animals and toxic chemicals, anemia, and developmental delays.

Homeless Children
The number of homeless children in the United States has increased by more than 35% since the recession began in 2007. An estimated 1.6 million children are homeless, living in shelters, with other relatives or on the streets.

Homeless children have an increased frequency of illness, including intestinal infections, anemia, neurologic disorders, seizures, behavioral disorders, mental illness, and dental problems, as well as an increased frequency of trauma and substance abuse. Homeless children are admitted to U.S. hospitals at a much higher rate than the national average. They have higher school failure rates, and the likelihood of their being victims of abuse and neglect is much higher. The limited research on homeless children suggests high rates of developmental delays, severe depression, or learning disorders. The increased frequency of maternal psychosocial problems, especially depression, in homeless households has a significant untoward impact on the mental and physical health of these children. Because families tend to break apart under the strain of poverty and homelessness, many homeless children end up in foster care. If their families remain intact, frequent moves make it very difficult for them to receive continuity of medical care or schooling.

Provision of adequate housing, job retraining for the parents, and mental health and social services are necessary to prevent homelessness from occurring. Physicians can have an important role in motivating society to adopt the social policies that will prevent homelessness from occurring by educating policymakers that these homeless children are at greater risk of becoming burdens both to themselves and to society if their special health needs are not met.

Runaway and Thrown-Away Children
Annually in the United States, an estimated 1.6-2.8 million youth run away. Several hundred thousand of these children have no secure and safe place to stay. Black and Hispanic youth, as well as lesbian, homosexual, bisexual, and transgender youth, are disproportionately represented in these numbers. The usual definition of a runaway is a youth younger than 18 yr who is gone for at least 1 night from his or her home without parental permission; ~70% of these youth endangers their physical well-being during the runaway episode. Most runaways leave home only once, stay overnight with friends, and have no contact with the police or other agencies. This group is no different from their "healthy" peers in terms of psychological status. A smaller but unknown number become multiple or permanent "runners" and are significantly different from the one-time runners, with less-favorable long-term outcomes.

Thrown-aways include children told directly to leave the household, children who have been away from home and are not allowed to return, abandoned or deserted children, and children who run away but whose caretakers make no effort to recover them or do not appear to care if they return. The same constellation of causes common to many of the other special-risk groups is characteristic of permanent runaways and thrown-aways, including environmental problems (family dysfunction, abuse, poverty) and personal problems of the young person (poor impulse control, psychopathology, substance abuse, or school failure). Thrown-aways experience more violence and conflicts in their families.

In the United States, it is a minority of runaway youths who become homeless street people. These youths have a high frequency of problem behaviors, with 75% engaging in some type of criminal activity and 50% engaging in prostitution. A majority of permanent runaways have serious mental problems; more than 33% are the product of families who engage in repeated physical and sexual abuse (see Chapter 40). These children also have a high frequency of medical problems, including hepatitis, sexually transmitted infections, and drug abuse. Although runaways often distrust most social agencies, they will come to and use medical services. Medical care may become the point of reentry into mainstream society and the path to needed services. U.S. parents who seek a physician's advice about a runaway child should be asked about the child's history of running away, the presence of family dysfunction, and personal aspects of the child's development. If the youth contacts the physician, the latter should examine the youth and assess the youth's health status, as well as willingness to return home. If it is not feasible for the youth to return home, foster care, a group home, or an independent living arrangement should be sought by referral to a social worker or a social agency. Although legal considerations involved in the treatment of homeless minor adolescents may be significant, most states, through their “Good Samaritan” laws and definitions of emancipated minors, authorize treatment of homeless youths. Legal barriers should not be used as an excuse to refuse medical care to runaway or thrown-away youths.

The issue of runaway youths is very complex in many developing nations, where in many instances the youth may be orphaned and/or leaving situations of forced sex or other abusive situations. It is estimated that there are tens of millions of such youth worldwide. Natural disasters such as the 2010 earthquake devastating Haiti also contribute to growing numbers of orphaned children. In 2012, there were an estimated 17.8 million HIV orphans globally, with 14.8 > 15 million in Africa. With school attendance <50% in many parts of sub-Saharan Africa, children who are orphaned are 17% less likely to attend school. Humanitarian and international organizations have begun to focus on this very vulnerable group of youths across the globe. Rates are often uncertain, and in many countries, these children have not even been recognized as an at-risk group, so great is the social chaos and so massive are the unmet needs.

Children Directly Affected By War and Other Forms of Direct Violence
See Chapter 39.2.

There have been ~250 major wars (defined as armed combat with more than 1,000 casualties) since the end of the Second World War.
The majority of these conflicts have been civil wars, many of which have lasted longer than a decade. Sixteen of the world’s poorest 20 countries have endured a civil war in the past 20 yr. Poorer countries are more likely to engage in war; a country whose median income is at the 50th percentile is one-half as likely to engage in a civil war as a country whose median income is at the 10th percentile. The distinction between intentional and unintentional injury loses its meaning in such situations; in modern wars, 70–80% of casualties are among women and children. Direct mortality and morbidity to children account for only a portion of war’s destructive impact on children. In 1996 the United Nations commissioned a report addressing the full consequences of war on children entitled “Promotion and Protection of the Rights of Children: Impact of Armed Conflict on Children” including (1) the disruption of basic educational and child health pediatric care and services; (2) hardships endured as a result of refugee status; (3) the abuse of the 250,000–300,000 children younger than age 18 yr who are soldiers; and (4) the impact on children when 1 or both parents are deployed to serve.

A growing number of children worldwide are facing acts of violence with a broad reach outside of the context of war, including religious crusades (such as suicide bombers in countries not always engaged in war), countries with extraordinarily high rates of violence (such as certain cities in South Africa and Mexico) and as a result of individuals with uncertain or confused personal motives, such as the mass shooting in an elementary school in Sandy Hook, Connecticut. While the direct consequences of such nonwar violence impact far fewer children than do those from war, the reach of such random acts of violence is increasingly touching a wider swath of our globe.

**Inherent Strengths in Vulnerable Children and Interventions**

By age 20–30 yr, many children in the United States and other developed countries who were at special risk will have made moderate successes of their lives. Teenage mothers and children who were born prematurely or in poverty demonstrate that, by this age, the majority have made the transition to stable marriages and jobs and are accepted by their communities as responsible citizens. As the numbers of risk factors increases for an individual, the odds for a successful adulthood decline.

Certain biologic characteristics are associated with success, such as being born with an accepting temperament. Avoidance of additional social risks is even more important. Premature infants or preadolescents with conduct disorders and poor reading skills, who must also face a broken family, poverty, frequent moves, and family violence, are at much greater risk than children with only 1 of these risks. Perhaps most important are the protective buffers that have been found to enhance children’s resilience because these can be aided by an effective healthcare system and community. Children generally do better if they can gain social support, either from family members or from a nonjudgmental adult outside the family, especially an older mentor or peer. Providers of medical services should develop ways to “prescribe” supportive “other” persons for children who are at risk. Promotion of self-esteem and self-efficacy is a central factor in protection against risks. It is essential to promote competence in some area of these children’s lives.

A team is needed because it is rare for 1 individual to be able to provide the multiple services needed for high-risk children. Successful programs are characterized by at least 1 caring person who can make personal contact with these children and their families. Most successful programs are relatively small (or are large programs divided into small units) and nontabulcratic but are intensive, comprehensive, and flexible. They work not only with the individual, but also with the family, school, community, and at broader societal levels. Introduction of remedial programs to children at the youngest possible age appears to increase the chance of success across multiple problem areas. It is also important for services to be continued over a long period.

**Global Warming**

Global climate change is occurring and will impact everyone; its impact will be harder felt on children and hardest felt are certain categories of vulnerable child, including those living in areas threatened by variations in rainfall, temperatures or hurricanes and cyclones (Fig. 1-6).

**The Challenge to Pediatricians**

Concerns about the aforementioned problems of children throughout the world have generated 3 sets of goals. The first set includes that all families have access to adequate perinatal, preschool, and family planning services; that international and national governmental activities be effectively coordinated at the global, regional, national, and local levels; that services be so organized that they reach populations at special risk; that there be no insurmountable or inequitable financial barriers to adequate care; that the healthcare of children have continuity from prenatal through adolescent age periods; and that every family ultimately have access to all necessary services, including developmental, dental, genetic, and mental health services. A second set of goals addresses the need for reducing unintended injuries and environmental risks, for meeting nutritional needs, and for health education aimed at fostering health-promoting lifestyles. A third set of goals covers the need for research in biomedical and behavioral science, in fundamentals of biotechnology and human biology, and in the particular problems of mothers and children.

**PATTERNS OF HEALTHCARE**

Healthcare utilization and organization differs significantly among nations, reflecting differences in the geography and wealth of the country; the priority placed on healthcare versus other competing needs and interests within a nation and by the international community; philosophy regarding prevention versus curative care; and the balance between child and adult healthcare needs. An interesting analysis of 2 industrialized countries (United States and Japan) revealed that for comparable symptoms, Japanese children were 2.5 times more likely to visit a community physician’s office or emergency clinic, and 11 times more likely to visit a hospital-based outpatient clinic. In most countries, hospitals are sources of both routine and intensive child care, with medical and surgical services that may range from immunization and developmental counseling to open heart surgery and renal transplantation. Clinical conditions and procedures requiring intensive care are also likely to be clustered in university-affiliated centers serving as regional resources—if these resources exist.

In developing countries, external forces may also contribute greatly to the organization of healthcare and possibly to healthcare utilization. This relationship is complex. The significant declines in infant and child mortality enjoyed in many of the developing countries in the past 4 decades have occurred in the context of support from the international community, including agencies such as UNICEF, WHO, and the World Bank; bilateral donors (the aid provided from 1 country to another); and nongovernmental agencies to develop integrated, universal primary pediatric care with an emphasis on primary (vaccination) and selected secondary (oral rehydration solution [ORS], treatment of pneumonia and malaria) prevention strategies. But, as
healthcare systems become dependent on such external support, their populations are increasingly vulnerable to changes in political will over which they have little or no influence.

In the United States, pediatricians report an average of 50 preventive care visits per wk, 33% for infants. The visits average 17-20 min, increasing in length as children become adolescents. The principal diagnoses, accounting for >40% of these visits, are well-child visits (15%), middle-ear infections (12%), and injuries (10%). Ambulatory visits by children and youth decrease with age. The opposite occurs with adults. Nonwhite children are more likely than white children to use hospital facilities (including the emergency room) for their ambulatory care; the number of well-child visits annually is almost 80% higher among white infants than black infants. Children with private insurance are more likely than children with public insurance who, in turn, are more likely than uninsured children to receive non–emergency room care. Insurance coverage increases outpatient utilization and receipt of preventive care by approximately 1 visit per year for children. Between 70 and 90 children per 1,000 children are hospitalized per year. These rates are less than those of adults up to age 65 yr, except for the first year of life. Children represent <7% of the total acute hospital discharges; in children's hospitals, ~70% of admissions are for chronic conditions, and 10-12% of pediatric hospitalizations are related to birth defects and genetic diseases. White children are less likely to be hospitalized than black or Hispanic children, but more likely than Asian children. Poor children are nearly twice as likely as nonpoor children to be hospitalized. Insurance coverage also appears to reduce hospital admissions that are potentially manageable in an ambulatory setting.

**PLANNING AND IMPLEMENTING A SYSTEM OF CARE**

Access to at least a basic level of quality services to promote health and treat illness is a right of every person. Having health insurance, whether private or governmental, is strongly associated with access to primary care. Efforts to make the delivery of healthcare more efficient and effective have led to the creation of new categories of healthcare providers, such as pediatric nurse practitioners in industrialized nations and trained birth attendants in developing countries, and to participate in new organizations for providing care to children, such as various managed care arrangements.

The U.S. Patient Protection and Affordable Care Act passed in 2010 and upheld by the United States Supreme Court in 2012, contains provisions specific to children, including a requirement that all preexisting conditions be covered and (effective 2014) pregnancy and newborn care be covered, as well as vision and dental care for children.

**Health Services for At-Risk Populations**

In the United States, the largest vulnerable group is children living in poverty, representing approximately 22% of U.S. children. Substantial proportions of children in other industrialized countries are also living in poverty. The approach to addressing the needs of this group in the United States has been the establishment of a targeted insurance program, Medicaid, which became law in 1965 as a jointly funded cooperative venture between the federal and state governments to assist states in the provision of adequate medical care to eligible needy persons. The federal statute identifies ≥25 different eligibility categories for which federal funds are available. These statutory categories can be classified into 5 broad coverage groups: children, pregnant women, adults in families with dependent children, individuals with disabilities, and individuals ≥65 yr old. Pediatric care in the United States is highly dependent on Medicaid; however, only a relatively small proportion of the Medicaid funds actually go to child healthcare, with the remainder serving older adults. Following broad national guidelines, each state establishes its own eligibility standards; determines the type, amount, duration, and scope of services; sets the rate of payment for services; and administers its own program. Although Medicaid has made great strides in enrolling low-income children, significant numbers of children remain uninsured. From 1988 to 1998, the proportion of children insured through Medicaid increased from 15.6% to 19.8%, but the percentage of children without health insurance increased from 13.1% to 15.4%. Minority children were disproportionately among those without insurance. The Balanced Budget Act of 1997 created a new children's health insurance program called the State Children's Health Insurance Program (SCHIP). This program gave each state permission to offer health insurance for children, up to age 19 yr, who are not already insured. SCHIP is a state-administered program and each state sets its own guidelines regarding eligibility and services. There is great variation by state, but in many states, the SCHIP program has begun to reduce racial inequities in access to healthcare for children. In 2009, the percent of children without insurance had decreased to 9%.

Many industrialized nations have adapted different “safety net” systems to assure adequate coverage of all youth. Many of these programs provide health insurance for all children, regardless of income, hoping to avoid problems with children losing insurance coverage and access to healthcare as a result of changes in eligibility by providing a single form of insurance that all providers accept. The response of developing countries to the issue of universal access to care for children has been uneven, with some providing no safety net, but many having limited universal or safety net services.

To address the special needs of Native Americans in the United States, the Indian Health Service, established in 1954, has been the responsibility of the Public Health Service, but the 1975 Indian Self-Determination Act gave tribes the option of managing Native American health services in their communities. The Indian Health Service is managed through local administrative units, and some tribes contract outside the Indian Health Service for healthcare. Much of the emphasis is on adult services: treatment for alcoholism, nutrition and dietetic counseling, and public health nursing services. There are also >40 urban programs for Native Americans, with an emphasis on increasing access of this population to existing health services, providing special social services, and developing self-help groups. In an effort to accommodate traditional Western medical, psychologic, and social services to the Native American cultures, such programs include the “Talking Circle,” the “Sweat Lodge,” and other interventions based on Native American culture (see Chapter 4). The efficacy of any of these programs, especially those to prevent and treat the sociopsychological problems particular to Native Americans, has not been determined.

Recognizing the health needs of migrants in the United States, the U.S. Public Health Service initiated in 1964 the Migrant Health Program to provide funds for local groups to organize medical care for migrant families. Many migrant health projects that were initially staffed by part-time providers and were open for only part of the year have been transformed into community healthcare centers that provide services not only for migrants but also for other local residents. As of 2012, there are >700 Migrant Health Centers and satellite sites operating in 42 states. Health services for migrant farm workers often need to be organized separately from existing primary care programs because the families are migratory. Special record-keeping systems that link the healthcare provided during winter months in the south with the care provided during the migratory season in the north are difficult to maintain in ordinary group practices or individual physicians' offices. Outreach programs that take medical care to the often remote farm sites are necessary, and specially organized Head Start, early education, and remedial education programs should also be provided. Approaches in other countries have also focused on business initiatives for migrant populations to enable them to overcome the cycle of financial dependency on their migratory lifestyle.

The United States has spent $14 billion through the 1987 McKinney-Vento Act to provide emergency food, shelter, and healthcare; to finance help for young runaways; to aid homeless people in making their way back into the housing market; and to place homeless children in school. Mobile vans, with a team consisting of a physician, nurse, social worker, and welfare worker, have been shown to provide effective comprehensive care, ensure delivery of immunizations, link the children to school health services, and bring the children and their families into a stable relationship with the conventional medical system. Special record-keeping systems have been introduced to enhance continuity and to provide a record of care once the family has moved to a
permanent location. Because of the high frequency of developmental delays in this group, linkage of preschool homeless children to Head Start programs is an especially important service. The Runaway Youth Act, Title III of the Juvenile Justice and Delinquency Prevention Act of 1974 (Public Law 93-414) and its amended version (Public Law 95-509) have supported shelters and provide a toll-free 24 hr telephone number (1-800-621-4000) for youths who wish to contact their parents or request help after having run away.

Other nations have expanded the reality of the "health safety net" for children. In Belgium, Finland, the Netherlands, Portugal, and Spain, the right to housing has been incorporated into the national constitutions. The Finnish government has devised a multifaceted response to the problem, including housing building, social welfare and healthcare services, and the obligation to provide a home of minimum standards for every homeless person. The number of homeless in Finland has been reduced by 50%.

Evaluation of Healthcare
The Institute of Medicine issued a report, "Crossing the Quality Chasm: A New Health System for the 21st Century" in 2001. This report, challenging American physicians to renew efforts to focus not just on access and cost, but also on quality of care, has been furthered in several pediatric initiatives, including, but not limited to, specific initiatives for monitoring child health outlined in the Institute of Medicine report "Children's Health, the Nation's Wealth"; challenge/demonstration grants funded by the Robert Wood Johnson Foundation; and the National Initiative for Children's Healthcare Quality. Importantly, each of these initiatives is calling for the establishment of measurable standards for assessment of quality of care and for the establishment of routine plans for periodic reassessment thereof. Efforts have been initiated at some medical centers to establish evidence-based clinical pathways for disorders (such as asthma) where there exists sound evidence to advise these guidelines. Pediatricians have developed tools to evaluate the content and delivery of pediatric preventive "anticipatory guidance," the cornerstone of modern pediatrics (see Chapter 5).

THE INFORMATION EXPLOSION OF THE 21ST CENTURY
There is no touchstone through which physicians can ensure that the process of their own continuing education will keep them abreast of advancing knowledge in the field, but the requirement for "Maintenance of Certification" as opposed to the former practice of lifelong certification by specialty boards actively addresses this issue (see Chapter 2). An essential element of this process may be for physicians to take an active role, such as participating in medical student and resident education. Efforts in continuing self-education will also be fostered if clinical problems can be made a stimulus for a review of standard literature, alone or in consultation with an appropriate colleague or consultant. This continuing review will do much to identify those inconsistencies or contradictions that will indicate, in the ultimate best interest of patients that things are not what they seem or have been said to be. These difficulties may be exacerbated by commercially sponsored education programs and research projects that may, on occasion, put profit before the patient's best interests. Physicians still learn most from their patients, but this will not be the case if they fall into the easy habit of accepting their patients' problems casually or at face value because the problems appear to be simple.

The tools that physicians must use in dealing with the problems of children and their families fall into 3 main categories: **cognitive** (up-to-date factual information about diagnostic and therapeutic issues, available on recall or easily found in readily accessible sources, and the ability to relate this information to the pathophysiology of their patients in the context of individual biologic variability), **interpersonal or manual** (the ability to carry out a productive interview, execute a reliable physical examination, perform a deft venipuncture, or manage cardiac arrest or resuscitation of a depressed newborn infant), and **attitudinal** (the physician's unselfish commitment to the fullest possible implementation of knowledge and skills on behalf of children and their families in an atmosphere of empathic sensitivity and concern). With regard to this last category, it is important that children participate with their families in informed decision making about their own healthcare in a manner appropriate to their stage of development and the nature of the particular health problem.

The workday needs of professional persons for knowledge and skills in care of children vary widely. Primary care physicians need depth in developmental concepts and in the ability to organize an effective system for achieving quality and continuity in assessing and planning for healthcare during the entire period of growth. They may often have little or no need for immediate recall of esoterica. On the other hand, consultants or subspecialists not only need a comfortable grasp of both common and uncommon facts within their field and perhaps within related fields, but also must be able to cope with controversial issues with flexibility that will permit adaptation of various points of view to the best interest of their unique patient.

At whatever level of care (primary, secondary, or tertiary) or in whatever position (student, pediatric nurse practitioner, resident pediatrician, practitioner of pediatrics or family medicine, or pediatric or other subspecialist), professional persons dealing with children must be able to identify their roles of the moment and their levels of engagement with a child's problem; each must determine whether his or her experience and other resources at hand are adequate to deal with this problem and must be ready to seek other help when they are not.

ORGANIZATION OF THE PROFESSION AND THE GROWTH OF SPECIALIZATION
The 20th century witnessed the formation of professional societies of pediatricians around the globe. Some of these societies, such as the American Academy of Pediatrics and the American Board of Pediatrics, are concerned with education and the awarding of credentials certifying competence and the continuing maintenance of competence as a pediatrician and/or a pediatric subspecialist to the public. From its inception in 1933 through the beginning of 2014, the American Board of Pediatrics certified 108,879 general pediatricians.

The amount of information relevant to child healthcare is rapidly expanding, and no person can become master of it all. Physicians are increasingly dependent on one another for the highest quality of care for their patients. Approximately 25% of pediatricians in the United States claim an area of special knowledge and skill, including >20,000 who have board certification in 1 of the 14 pediatric subspecialties with board certification. Each year approximately 10% of the ~3,000 pediatric residents training in the United States are enrolled in a dual-residency training program that will lead to eligibility for board certification in both pediatrics and internal medicine.

In the United States, most subspecialists practice in academic settings or children's hospitals. Likewise, specialists are growing in number in other industrialized countries and in developing nations that are becoming industrialized. Reflecting the diverse cultures, organization of medical care, economic circumstances and the history of medicine within each of the ~200 countries across the globe, is the great diversity in role of pediatricians within the healthcare delivery system to children in each country; Figure 1-7 illustrates the resultant variations in pediatricians per population among some European countries.

Beyond certifying bodies, there are other pediatric societies primarily concerned with organizing members of the profession in their country or region to dedicate their efforts, advocacy and resources toward children. In the United States, the American Academy of Pediatrics currently has a membership of ~60,000 child health specialists in both academic and private practice. Most general pediatricians in the United States enter private practice; ~66% are in group practices, 5% enter solo practice, and 5% work in a health maintenance organization. The American Academy of Pediatrics provides a variety of continuing educational services to pediatricians in multiple national and regional settings and tracks the professional activities and practices of its members. A comparable group in India, the Indian Academy of Pediatrics, was formed in 1963, and now has ~16,500 members and 16 subspecialty chapters. Likewise, the Pakistani Pediatrics Association was founded in 1967, the Malaysian
Pediatric Association was started in 1985, and the Canadian Pediatric Society was founded in 1922. Established in 1974, the Asian Pacific Pediatric Association includes 20 member pediatric societies from throughout eastern Asia, and the International Pediatric Association established in 1910 includes 144 national pediatric societies from 139 countries, 10 regional pediatric societies, and 11 international pediatric specialty societies. The European Academy of Pediatrics is the pediatric specialist organization for the member countries of the European Union and the European Free Trade Association, and the Pediatric Council of the Arab Board of Medical Specializations is the comparable institution for 19 of the world’s Arab nations. These societies represent but a few of the many national and regional pediatric professional organizations around the world who seek to identify and bring treatments and approaches supporting child well-being to pediatricians worldwide.

Bibliography is available at Expert Consult.

1.1 Innovations in Addressing Child Health and Survival in Low-Income Settings

Zulfiqar Ahmed Bhutta

GLOBAL BURDEN AND MORTALITY TRENDS

The current global burden of neonatal and child death is largely concentrated in Central and sub-Saharan Africa and South Asia (Figs. 1-8 and 1-9; see also Fig. 1-1 and Table 1-1). Ten countries have almost 3/4 of the global burden of maternal and newborn deaths as well as stillbirths.

It is estimated that 6.2 million children younger than 5 yr died in 2012, a 63% reduction from 16.9 million in 1970. However, there are still wide disparities and in 2012, child mortality rates range from a high of 182 per 1,000 in Sierra Leone to 2 per 1,000 in Iceland and Luxembourg. Progress in this regard has been variable, and despite global progress, of the 75 countdown countries that have almost 98% of all maternal and under-5 child deaths, only 13 are on track to reach MDG targets for child mortality. Other global estimates from the Institute of Health Metrics and Evaluation indicate that only 31 developing countries will reach MDG 4 targets by 2015.

From 1990 to 2013, annual rates of decline ranged from 6.7% to −0.9%. In 2013, neonatal deaths account for 41.3% of under-5 deaths, up from 37.6% in 1990. Comparing 2013 with 1990, rising numbers of births, particularly in sub-Saharan Africa, were associated with an additional 1.5 million child deaths. Neonatal mortality reduction has been much slower than that for maternal and child (1-59 mo) mortality, and slowest in the highest burden countries, especially in Africa. The sobering realization is that even in countries that would reach their MDGs 4 and 5 targets, many would still have high numbers of deaths with much scope for improvement.

CAUSES OF NEWBORN AND CHILD DEATHS

The Child Health Epidemiology Reference Group estimated that 40.3% of 7.6 million under-5 deaths in 2010 occurred in the newborn period; 2013 figures from the Institute of Health Metrics and Evaluation corroborate these estimates.

Among newborn deaths, major causes include preterm birth complications (14.1%; 1.078 million), intrapartum-related complications, previously labeled as birth asphyxia (717,000 deaths; 9.4%), and sepsis or meningitis (393,000; 5.4%) neonatal deaths. Among older children, the leading causes of deaths included pneumonia (14.1%; 1.071 million), diarrhea (9.9%; 751,000), and malaria (7.4%; 564,000) (Fig. 1-10A). Existing data suggest broadly comparable figures for under-5 deaths (Fig. 1-10B), although some categories are different, notably higher proportion of malaria deaths among under-5 children in the Global Burden of Disease study 2010 estimates and lower numbers for pneumonia deaths.

An unaddressed burden of stillbirths exists globally and is not included in the current Global Burden of Disease study estimates. Of an estimated 2.64 million stillbirths worldwide in 2009, 76.2% occurred in south Asia and sub-Saharan Africa, mostly among rural populations. An estimated 45% of these stillbirths occur in the intrapartum period, reflecting a clear extension of the neonatal deaths related to intrapartum events, previously labeled as birth asphyxia deaths. The highest risk time is around birth, when more than 40% of maternal deaths and combined stillbirths during labor and neonatal deaths occur. These deaths occur rapidly, requiring urgent response by healthcare workers. Table 1-5 lists the top 10 countries for risks of intrapartum stillbirths and newborn deaths on the first day of life.
Chapter 1 ♦ Overview of Pediatrics

Bibliography
Figure 1-8 Neonatal deaths by country (rates). (From Bhutta ZA, Black RE. Global maternal, newborn, and child health—so near and yet so far. N Engl J Med 2013;369:2226–2235.)

Deaths in Children <5 Yr of Age per 1,000 Live Births in 2011

Figure 1-9 Child (1-4 yr) deaths per 1,000 live births. (From Bhutta ZA, Black RE. Global maternal, newborn, and child health—so near and yet so far. N Engl J Med 2013;369:2226–2235.)

Being born small, because of preterm birth or small for gestational age (SGA) or both, is the leading risk factor for neonatal deaths and carries increased risk for postneonatal mortality, growth failure, and adult-onset noncommunicable conditions (see Chapter 97). South Asia has the highest SGA rates and sub-Saharan Africa has the highest preterm birth rates. Babies who are term SGA low birthweight face risks for stunting, and adult-onset metabolic conditions. Fifteen million preterm births, especially those <32 wk gestation, are at highest risk of neonatal death, with ongoing postneonatal mortality risk, significant risk of long-term neurodevelopmental impairment, and stunting, as well as noncommunicable conditions. Four million neonates annually have other life-threatening conditions, including intrapartum-related
Poverty is a huge barrier and affects all levels of care because much of the burden of maternal and child mortality and ill health is concentrated among the poorest countries of sub-Saharan Africa and South Asia. In many of these countries, the bulk of the mortality is clustered among the poor, frequently residing in remote and rural populations with limited access to healthcare services. A sizeable proportion of deaths also occur among the urban poor living in slum conditions with limited social support networks and poor living conditions. Other determinants, such as environmental factors (e.g., overcrowding, poor air quality and sanitary conditions), may be much worse in urban slums than in many rural populations. Lack of trained human resources and transportation facilities in rural populations, as well as quality of care in existing primary care settings are also problems. Figures 1-11 and 1-12 illustrate some of the inequities observed across key evidence-based maternal and child interventions across and within large number of developing countries. Interventions that have a relatively narrow brain injury, severe bacterial infection, and pathologic jaundice, with 1.4 million neonates surviving with long-term neurodevelopmental impairment. The consequences of not acting to improve birth outcomes by 2035 are estimated at 116 million deaths, 99 million with disability or lost development potential, and many millions of adults with noncommunicable disease following being born SGA and or prematurely.

**UNDERSTANDING SOCIAL DETERMINANTS AND BARRIERS FOR CARE**

Understanding the causes of deaths allows for better planning and targeting of interventions. Between 2000 and 2010, the bulk of the reduction in under-5 child mortality related to decreases in pneumonia, measles, and diarrhea deaths, whereas corresponding reductions in neonatal causes of deaths other than tetanus (notably those associated with prematurity and intrapartum related events) was minimal.

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>RISK OF NEONATAL DEATH ON DAY OF BIRTH (PER 1,000 LIVE BIRTHS)</th>
<th>INTRAPARTUM STILLBIRTH RATE (PER 1,000 TOTAL BIRTHS)</th>
<th>INTRAPARTUM STILLBIRTHS AND NEONATAL DEATHS ON DAY OF BIRTH (PER 1,000 TOTAL BIRTHS)</th>
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</thead>
<tbody>
<tr>
<td>Pakistan</td>
<td>15</td>
<td>26.4</td>
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<td>Nigeria</td>
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<tr>
<td>Somalia</td>
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<td>14.0</td>
<td>29.7</td>
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<td>Guinea-Bissau</td>
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<tr>
<td>Bangladesh</td>
<td>9</td>
<td>20.6</td>
<td>28.9</td>
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<tr>
<td>Democratic Republic of Congo</td>
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<tr>
<td>Lesotho</td>
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<td>11.8</td>
<td>27.5</td>
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<tr>
<td>Angola</td>
<td>16</td>
<td>11.7</td>
<td>27.4</td>
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</tbody>
</table>
commodities by well-trained and motivated care providers. quality of care within facilities and ensure availability of life-saving within the public health system. There is also the need to preclude care seeking and access where such care is not freely available.

shortage of health workers up coverage, especially in circumstances where there is widespread. shifting strategies have been shown to yield beneficial results in diverse income, education, and technology shift alone.

Estimates of the impact of various factors on child survival between 1990 and 2013 indicate that while rising numbers of births, particularly in sub-Saharan Africa, led to 1.5 million more child deaths, rising income per capita and maternal education led to 774,000 and 2.4 million fewer deaths, respectively. Technology change alone led to 4.0 million fewer deaths. In 23 developing countries, there is evidence that declines since 2000 have been faster than predicted on the basis of income, education, and technology shift alone.

**EVIDENCE-BASED INTERVENTIONS AND INNOVATIONS TO ADDRESS INEQUITIES**

There is a range of preventive, promotive and therapeutic interventions that can affect newborn and child survival (Table 1-6).

These services require appropriate delivery platforms for scaling up coverage, especially in circumstances where there is widespread shortage of health workers, and the removal of financial barriers that preclude care seeking and access where such care is not freely available within the public health system. There is also the need to improve quality of care within facilities and ensure availability of life-saving commodities by well-trained and motivated care providers.

**COMMUNITY HEALTH WORKERS FOR NEWBORN AND CHILD HEALTH**

The global shortage of a skilled health workforce has been a key barrier to effective coverage and in many instances policy makers and planners resort to the use of community health workers (CHWs) who are provided basic training in preventive and promotive strategies. Such task-shifting strategies have been shown to yield beneficial results in diverse settings, frequently in malaria and HIV management. Communities should take active part in improving their own health, and the dynamic role of CHWs in delivery of health-related care are well recognized.

CHWs work in liaison with frontline health workers and are fastened across the primary healthcare for better success in reaching the goals (Fig. 1-13).

A growing array of interventions delivered by CHWs can significantly improve neonatal and child health and survival; behavioral interventions to promote healthy behavior; preventive interventions, such as immunization; and more complex tasks, such as case management of childhood illnesses (e.g., pneumonia, malaria, and neonatal sepsis). The active involvement and empowerment of communities through CHWs have positive effects on health by changing health beliefs and improving care seeking for illnesses. CHWs increase the proportion of people who receive healthcare and increase the number of children with up-to-date immunization statuses. CHWs who provide some amount of support of breastfeeding, as well as care during pregnancy, help reduce child mortality through various antenatal interventions, including pregnancy surveillance, vitamin supplementation, and promotion of birth preparedness. CHW programs are also dependent upon basic tool kits and a steady and reliable supply of key commodities. Lack of adequate supplies and frequent stock outs are a major impediment to effective programs and implementation.

Women's and community support groups which are largely formulated and facilitated by CHWs have shown reductions in neonatal mortality and morbidity and improvement in domiciliary practices, such as early initiation of breastfeeding and healthcare seeking for their illnesses. These participatory activities empower mothers, emphasize safe delivery practices and encourage care seeking behavior.

Home visits by CHWs may improve coverage of key newborn care practices such as early initiation of breastfeeding, exclusive breastfeeding, skin-to-skin contact, delayed bathing and attention to hygiene, such as hand washing with soap and water, clean umbilical cord care, immunization and early diagnosis, detection of complications,
and appropriate referrals. Home-based newborn care consisting of therapeutic interventions, case management and referrals, and preventative interventions such as health education have shown reductions in neonatal mortality and in stillbirths.

Implementation of an essential newborn care package along with administration of home-based antibiotic therapy for suspected neonatal sepsis by CHWs has resulted in a 62% reduction in the neonatal mortality rate when 93% of the newborns in the intervention area were provided treatment. In a meta-analysis of trials of community-based case-management of pneumonia all-cause neonatal mortality was 27% lower in the intervention group, whereas pneumonia-specific neonatal mortality in the intervention group was reduced by an even greater amount. Case management of children suffering from pneumonia, malaria, and diarrhea may be the potential way forward in the low-income setting. Case management of pneumonia by CHWs could result in a 70% reduction in mortality from pneumonia in children <5 yr of age. Community-based interventions correlate to a 13% and 9% increase in care seeking for pneumonia and diarrhea, respectively. Case management is associated with increased uptake of ORS and zinc for management of diarrhea. These interventions also lead to a 32% reduction in pneumonia-specific mortality. CHWs can also be trained to perform rapid diagnostic tests for malaria, and manage test-positive children with antimalarials.

CHWs can also play a role in improving the use of anthelmintics in children. Interventions such as preventive chemotherapy, health education to promote general hygiene and sanitation, iron and β-carotene supplementation, construction of latrines, removing cattle from residential areas, staff training and community mobilization can have significant impacts on prevention and management of worm infestations. Evidence suggests that school-based delivery of anthelmintics can significantly reduce soil-transmitted helminthes prevalence, schistosomiasis prevalence, and anemia. Interventions related to handwashing counseling (for individuals or groups) suggested a 30% reduction in the risk of diarrhea as well.

**THE ROLE OF INFORMATION TECHNOLOGY AND mHEALTH PLATFORMS**

Mobile health, or mHealth, is the use of mobile information and communication technologies for improving health. It can be used for a wide range of purposes, including health promotion and illness prevention, healthcare delivery, training and supervision, electronic payments, and information systems. This is widely regarded as a great equalizer across social strata in increasing access to information and empower health workers to reach marginalized populations. In the simplest forms SMS/text-based campaigns can be an effective way to share health information with people who lack reliable Internet access and in other instances telemedicine can permit specialist access and consultations which were hitherto not possible because of geographic constraints and limitations. mHealth is of particular interest in low- and middle-income countries, where widespread mobile networks and access to devices are connecting people, leap-frogging older technologies to dramatically improve information flow, data collection, social and behavior change, and emergency response.

**CASH TRANSFERS TO REDUCE POVERTY BARRIERS AND IMPROVE CHILD HEALTH**

Out of pocket expenses by households form the major share of total health expenditure in most low income countries and a substantial share in middle income countries. Financial incentives are becoming widely used to improve healthcare coverage, alleviate poverty and improve access to child health services. Some support platforms have a dual purpose of reducing financial barriers and also strengthening service delivery. Financial incentive programs may include conditional/unconditional cash transfers, conditional/unconditional microcredit, conditional/unconditional voucher, user fee removal and health insurances. Financial incentive programs targeting child health generally focus on breastfeeding practices; vaccination; healthcare use; management of diarrheal diseases; and other preventive health interventions including preventive deworming, vitamin A and iron supplementation. These programs are also directed toward education improvement by improving school enrollment, attendance, and occasionally some measure of performance.

**OTHER TECHNOLOGIES AND INNOVATIONS**

There has been a massive increase in global knowledge and potential of low-cost technologies to improve diagnosis and care of sick newborn infants and children. These span bedside tools to assess risk of severe
### Evidence-based Interventions to Address Newborn and Child Health and Undernutrition

<table>
<thead>
<tr>
<th>NEWBORN</th>
<th>NUTRITION</th>
<th>DIARRHEA</th>
<th>PNEUMONIA</th>
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<tbody>
<tr>
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<td>Preventive vitamin A supplementation</td>
<td>Preventive zinc supplementation</td>
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<td>Periconceptional folic acid supplementation or fortification</td>
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<td>Multiple micronutrient/iron-folate supplementation in pregnancy</td>
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<td>Antibiotics for dysentery</td>
<td>ORS</td>
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<td>Appropriate complementary feeding</td>
<td>Zinc for treatment of diarrhea</td>
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<td>Tetanus toxoid vaccination</td>
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<td>Induction of labor for pregnancies after 41 weeks</td>
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<td>Labor and delivery management</td>
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<td>Antibiotics for preterm premature rupture of membranes</td>
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<td>Immediate assessment and stimulation</td>
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<td>Clean postnatal practices</td>
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<td>Hospital care of preterm babies including Kangaroo mother care</td>
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ANS, antenatal corticosteroid treatment; Hib, Haemophilus influenzae type b; IPTp, intermittent preventive treatment of malaria for pregnant women.

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**Figure 1-13** Neonatal and child health interventions: delivered by community health workers.
illness such as handheld pulse oximetry devices for children with respiratory infections, development of 4% chlorhexidine gel for prevention of cord infections in newborns, and injection devices to aid health workers such as Uniject systems.

There has been considerable work to achieve consensus across a range of UN agencies, academic bodies, and professional groups on key essential evidence-based interventions for maternal and child health that need implementation and scaling up within health systems.

*Bibliography is available at Expert Consult.*
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The Partnership for Maternal Newborn & Child Health: A global review of the key interventions related to reproductive, maternal, newborn and child health (RMNCH), Geneva, Switzerland, 2011.


The knowledge. This definition incorporates 2 key concepts related to the concept of desired health outcomes and are consistent with current professional practice—a chasm made wider by variations in practice and disparities in care from doctor to doctor, institution to institution, geographic region to geographic region, and socioeconomic group to socioeconomic group.

Historically, success in medicine was viewed as advances in technology, identification of new treatments, and the generation of new evidence to improve care. Although these facets of medical advances continue to be important, it is estimated that it takes about 17 yr for new knowledge and research findings to be adopted into clinical practice. Further, the Institute of Medicine’s (IOM) report “To Err is Human: Building a Safer Health System,” highlights that ~44,000–98,000 patients die in U.S. hospitals each year because of preventable medical errors. These errors were more likely to occur in environments such as operating rooms, emergency departments, and intensive care units. Preventable medical errors have an economic cost of $17–$29 billion per year. These gaps in quality and related high costs will only be solved when physicians and healthcare systems adopt the emerging new science of Quality Improvement (QI).

The need for QI is expanding even further. With the growing concerns of healthcare costs and also the implementation of the Affordable Care Act, the scope of QI has expanded from the level of individual patients to include the notion of the Triple Aim proposed by the Institute for Healthcare Improvement—improving the care for individual patients, improving the care for populations, and improving the cost effectiveness for healthcare delivery. Recently, there has been a recognition that QI needs to shift from the sphere of process improvement toward outcomes improvement, and to ensure value from the standpoint of the patient.

WHAT IS QUALITY?
The IOM defines quality of healthcare as the degree to which healthcare services for individuals and populations increases the likelihood of desired health outcomes and are consistent with current professional knowledge. This definition incorporates 2 key concepts related to healthcare quality: the direct relationship between the provision of healthcare services and health outcomes, and the need for healthcare services to be based on current evidence.

To measure healthcare quality, the IOM has identified Six Dimensions of Quality all of which relate to quality of care. The Six Dimensions of Quality are effectiveness, efficiency, equity, timeliness, patient safety, and patient-centered care. Quality of care needs to be effective, which means that healthcare services should result in benefits and outcomes. Healthcare services also need to be efficient, which incorporates the idea of avoiding waste and improving system cost efficiencies. Healthcare quality should improve patient safety, which incorporates the concept of patient safety as one of the key elements within the Six Dimensions of Quality. Healthcare quality must be timely, thus incorporating the need for appropriate access to care. Healthcare quality should be equitable, which highlights the importance of minimizing variations as a result of ethnicity, gender, geographic location, and socioeconomic status. Healthcare quality should be patient-centered, which underscores the importance of identifying and incorporating individual patient needs, preferences, and values in clinical decision making.

The IOM framework of the Six Dimensions of Quality emphasizes the concept that all Six Dimensions of Quality need to be met for the provision of high quality healthcare. These concepts can be viewed as the overall value proposition—that is, the value created for a patient. From the standpoint of the practicing physician, these Six Dimensions of Quality can be categorized into clinical quality and operational quality. To provide high-quality care to children, both aspects of quality—clinical and operational—must be met. Historically, physicians have viewed quality to be limited in scope to clinical quality with the goal of improving clinical outcomes, and have considered efficiency optimization and access as the role of healthcare plans, hospitals, and insurers. Healthcare organizations, which are subject to regular accreditation requirements, viewed the practice of clinical care delivery as the responsibility of physicians and limited their efforts to improve quality largely to process improvement to enhance efficiencies. This is further magnified as many office-based pediatricians have independent clinical practices and interact with hospitals only when they care for hospitalized children.

This traditional perspective is changing. The evolving healthcare system requires physicians, healthcare providers, healthcare organizations, and hospitals to partner together to measure, demonstrate, and improve the overall quality of care to the patients they serve. With many regulatory and accreditation changes such as Maintenance of Certification (MOC) requirements of the American Board of Pediatrics and the planned Maintenance of Licensure by U.S. state licensing bodies, physicians will be required to understand and implement QI principles into their clinical practice and report the quality of their care delivered by them in a transparent manner.

The recently implemented Patient Protection and Affordable Care Act has at its core quality measurement and QI. The Affordable Care Act aims at enhancing access to care which is a quality dimension. Quality measurement is integral to ensuring transparency and choice across health plans. An important concept for quality within the Affordable Care Act relates to expanding the conventional scope of quality to population health.

Definitions of Quality-Related Terms
Quality includes many concepts—quality measurement, quality reporting and benchmarking, process improvement, performance, and outcomes improvement using quality initiatives (Table 2-1).

FRAMEWORK FOR QUALITY
Quality is broader in scope than QI. As adopted by the American Academy of Pediatrics, the approach to quality includes 4 building blocks (Fig. 2-1). First, the standard for quality must be defined (i.e., developing evidence based guidelines, best practices, or policies that guide the clinician for the specific clinical situation). These guidelines should change based upon new evidence. For example, in 2000-2001, the American Academy of Pediatrics had published guidelines for care
Guidelines must adopt a high level of transparency in the development process. This is particularly relevant in the pediatric setting where there may be limited research using methods such as randomized controlled trials which would have a high level of rating from an evidence standpoint. As guidelines and policies related to quality need to be interpreted for specific settings, they should not be interpreted as standards of care.

### Developing Guidelines to Establish the Standard for Quality

Guidelines need to be developed based upon accepted recommendations, such as the Grades of Recommendation Assessment, Development and Evaluation system for rating the quality of evidence and strength of evidence which is crucial for guideline development. Guidelines must adopt a high level of transparency in the development process. This is particularly relevant in the pediatric setting where there may be limited research using methods such as randomized controlled trials which would have a high level of rating from an evidence standpoint. As guidelines and policies related to quality need to be interpreted for specific settings, they should not be interpreted as standards of care.

### Improving Quality

Achieving QI requires the adoption of a 3-step model: “Data → Information → Improvement.” Quality needs to be measured. Quality data obtained from the measurement then needs to be converted into meaningful information that can be compared and reported. This quality measurement must also be actionable to achieve improvements in clinical practice. QI is a rapidly growing science. There are currently 4 techniques available for QI.

### Model for Improvement

The Model for Improvement can be implemented using a framework of rapid cycle improvement also known as the plan-do-study-act (PDSA) cycle (Fig. 2-2). The PDSA cycle is typically aimed at testing small changes and then studying the results to plan and implement the next cycle of change (i.e., multiple PDSA cycles build on previous learning from PDSAs). Valuable information can be obtained from PDSA cycles that are successful, and those that are not, to help plan the next iteration of the PDSA cycle. The PDSA cycle specifically requires that improvements be data driven. This is important because many clinicians attempt to make changes for improvement in their practice but do not emphasize the importance of data collection.

The Model for Improvement has been successfully used in the Vermont Oxford Network (VON) to achieve improvements in care in of children with attention-deficit/hyperactivity disorder. Subsequently, in 2011, these were updated to highlight a greater emphasis on behavioral interventions rather than pharmacologic options.
the neonatal intensive care unit (NICU) setting. The VON is a global network of collaborating NICUs involved in several studies that have favorably impacted the care of newborns. An example of a successful VON QI effort is a project aimed at reducing rates of chronic lung disease in extremely low birthweight infants. Clinical teams participating in this improvement effort used special reports from the VON database, reviewed the available evidence with content faculty experts, and then identified improvement goals. The teams received QI training through conference calls and emails for a period of 1 year. This effort resulted in a 37% increase in early surfactant administration for preterm infants achieving a high degree of QI.

Another example of a successful QI collaborative using the improvement model relates to the reduction of catheter-associated bloodstream infections (CA-BSIs) in the pediatric intensive care unit (PICU) setting. Similar to the VON experience, this effort included a group of PICUs that collaborated to impact a serious preventable problem in the PICU—CA-BSIs. National content experts and local PICU quality champions monitored and provided performance data at the local level in an almost real-time basis to ensure continued learning and improvement. The engagement of the entire PICU team—physicians, trainees, nurses, respiratory therapists, and others created a culture of quality and accountability. There was a strong emphasis on team learning across the participating institutions. This national collaborative sponsored by the Children’s Hospital Association and the American Board of Pediatrics has resulted in a significant measurable reduction in CA-BSI rates across PICUs in the United States and is now in subsequent iterations of the PDSA cycle.

**Six Sigma**

Six Sigma relates to the reduction in undesirably variation in processes (Fig. 2-3). Every process has some level of inherent variation built into it. There are 2 types of variations in a process. Random variation relates to the variation that is inherent in the process simply because the process is being performed by humans. A physician completing a history and physical for a patient more than once may have a slightly different process each time, even though it is the same patient and the same physician. Random variation in processes is acceptable. In contrast, special cause variation relates to nonrandom variation that can adversely affect a process; when tracking infection rates in a nursery, a sudden increase in the infection rates may be secondary to poor handwashing techniques by a new healthcare provider in the system. This would represent a special cause variation (i.e., once this practice is improved, the infection rates will likely go back to the baseline level). Six Sigma attempts to provide a structured approach to unwanted variations in healthcare processes (Fig. 2-4). Six Sigma approaches have been successfully used in healthcare to improve processes in both the clinical and nonclinical settings.
methods have been successfully used in several outpatient and inpatient settings with resulting improvements in efficiency. Lean principles have also been adopted as a core strategy for children’s hospitals with the goal of improving efficiencies and reducing waste.

Management Sciences
Management sciences, also known as operations management, stems from operations research and relates to the use of mathematical principles to maximize efficiencies within systems. Management sciences has been successfully used in many non-healthcare settings, such as airlines and the military. Management sciences principles have been successful in many European healthcare settings to optimize efficiencies in outpatient primary care office settings, inpatient acute care hospital settings, surgical settings including operating rooms, and also for effective planning of transport and hospital expansion policies. Management sciences principles are being explored for use in the U.S. healthcare system. One of the techniques for management sciences, discrete event simulation was used at the Children’s Hospital of Wisconsin to effectively plan the expansion of the pediatric critical care services with the goal of improving quality and safety. The discrete event simulation model illustrated in Figure 2-6 depicts the various steps of the process in a PICU. Patients stratified across 3 levels of severity (low, medium, high) are admitted to the PICU, are initially seen by a nurse and physician, then stay in the PICU with ongoing care being provided by physicians and nurses, and are finally discharged from the PICU. The discrete event simulation model is a computer model developed using real estimates of numbers of patients, numbers of physicians and nurses in a PICU, and patient outcomes. Discrete event simulation models are created using real historical data, which allows testing the “what if” scenarios, such as the impact on patient flow and throughput by increasing the number of beds and/or changing nurse and physician staffing.

Another management sciences technique developed in Europe relates to the concept of cognitive mapping. Cognitive mapping aims at measuring the soft aspects of management sciences as illustrated in Figure 2-7. Cognitive mapping highlights the importance of perceptions and constructs of healthcare providers and how these constructs are linked in a hierarchical manner. Goals and aspirations of individual healthcare providers are identified by structured interviews and are mapped to strategic issues and problems, and options. By using specialized computer software, complex relationships can be identified to better understand the relationships between different constructs in a system. A discrete event simulation model views patient throughput based on numbers of beds, physicians, and nurses, and accounts for differences in patient mix. It does not account for many other factors, such as individual unit characteristics related to culture. By interviewing healthcare providers, cognitive maps can be developed that can help to better inform decision making.

MEASURING QUALITY
Robust quality indicators should have clinical and statistical relevance. Clinical relevance ensures that the indicators are meaningful in patient care from the standpoint of patients and clinicians. Statistical relevance ensures that the indicators have measurement properties to allow an acceptable level of accuracy and precision. These concepts are captured in the national recommendations that quality measures must meet the criteria of being valid, reliable, feasible, and usable (Table 2-2). Validity of quality measures relates to the notion that the measure is estimating the true concept of interest. Reliability relates to the notion that the measure is reproducible and provides the same result if retested. It is important that quality measures are feasible in practice. Quality measures must be useable, which means that they should be clinically meaningful. The Agency for Healthcare Research and Quality and the National Quality Forum have provided specific criteria to be considered when developing quality measures.

Quality indicators can be aimed at measuring the performance within 3 components of healthcare delivery: structure, process, and outcome (Fig. 2-8). Structure relates to the organizational characteristics in healthcare delivery. Examples of organizational characteristics are the number of physicians and nurses in an acute care setting and the availability and use of systems such as electronic health records. Process-related measures estimate how services are provided. Examples of a process measures are the percent of families of children with asthma who receive an asthma action plan as part of their office visit or the percent of hospitalized children who have documentation of

![Figure 2-6 Management sciences—discrete event simulation. PICU, pediatric intensive care unit.](image-url)
pain assessments as part of their care. Outcome measures relate to the final health status of the child. Examples of outcome measures are risk adjusted survival in an intensive care unit setting, birthweight-adjusted survival in the NICU setting, and functional status of children with chronic conditions such as cystic fibrosis.

It is important to distinguish between measures for accountability and measures for improvement. As illustrated in Figure 2-9, measures, particularly measures for accountability that may be linked to attribution and payment, must be based upon a rigorous process. This can be resource intensive and time-consuming. In contrast, measures for improvement serve a different purpose—to track incremental improvements linked to specific QI efforts. These may not undergo rigorous testing, but they have limited applicability beyond the specific QI setting.

Quality data can be quantitative and qualitative. Quantitative data includes numerical data, which can be continuous (patient satisfaction scores represented as a percentage with higher numbers indicating better satisfaction) or categorical (patient satisfaction scores obtained from a survey where a Likert scale is used indicating satisfactory, unsatisfactory, good, or superior care). Data can also be qualitative in nature, which includes nonnumeric data. Examples of qualitative data can include results from open-ended surveys related to the satisfaction of care in a clinic or hospital setting. It is important to be sensitive to the source and quality of data being obtained to ensure data quality.

Data measuring quality of care can be obtained from a variety of sources, which include chart reviews, patient surveys, existing administrative data sources (billing data from hospitals), disease and specialty databases, and patient registries, which track individual patients over time.

It is important to distinguish between databases and data registries. Databases are data repositories that can be as simple as a Microsoft Excel spreadsheet or as complex as relational databases using sophisticated servers and information technology platforms. Databases can provide a rich source of aggregated data for both quality measurement and research. Data registries allow tracking individual patients over time; this dynamic and longitudinal characteristic is important for population health management and QI.

<table>
<thead>
<tr>
<th>Table 2-2</th>
<th>Properties of Robust Quality Measures</th>
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<tr>
<td><strong>ATTRIBUTE</strong></td>
<td><strong>RELEVANCE</strong></td>
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<tr>
<td>Validity</td>
<td>Indicator accurately captures the concept being measured.</td>
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<tr>
<td>Reliability</td>
<td>Measure is reproducible.</td>
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<tr>
<td>Feasibility</td>
<td>Data can be collected using paper or electronic records.</td>
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<tr>
<td>Usability</td>
<td>Measure is useful in clinical practice.</td>
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**Figure 2-7** Management sciences—cognitive mapping.

**Figure 2-8** Donabedian model.

**Figure 2-9** Development of a quality measure.
Data quality can become a significant impediment when using data from secondary sources, which can adversely impact the overall quality evaluation. Once data on the quality indicator has been collected, quality measurement can occur at 3 levels: (1) measuring quality status at 1 point in time (e.g., percent of children seen in a primary care office setting who received the recommended 2-year immunizations); (2) tracking performance over time (e.g., change in immunization rates in the primary care office setting for children 2 yr of age); and (3) comparing performance across clinical settings after accounting for epidemiologic confounders (e.g., immunization rates for children <2 yr of age in a primary care office setting stratified by race and socioeconomic status as compared to the rates of other practices in community and rates at national levels).

Pediatric quality measures are being developed nationally. Table 2-3 lists some of the important currently endorsed pediatric national quality indicators.

### ANALYZING QUALITY DATA

Three approaches have been used for analyzing and reporting data. The classic approach from a research paradigm has been applied to quality data for statistically comparing trends over time, and differences before and after an intervention. P-values are interpreted as being significant if ≤0.05, which suggests that the likelihood of seeing a difference as extreme as observed has a probability of 5% (type I error). Another approach from an improvement science paradigm uses techniques such as run charts and control charts to identify special-cause variation. Special-cause variation attempts to capture observations that are unlikely to reflect random variation. Finally, quality data also has been reported on an individual patient level. This has gained popularity in the patient safety arena where identifying individual patient events in the form of descriptive analysis (“stories”) may be more powerful in motivating a culture of change, rather than statistical reporting of aggregate data in the form of rates of adverse patient safety events.

### COMPARING AND REPORTING QUALITY

There is an increasing emphasis on quality reporting in the United States. Many states have mandatory policies for the reporting of quality data. This reporting may be tied to reimbursement using the policy of P4P. P4P implies that reimbursements by insurers to hospitals and physicians will be partially based on the quality metrics. P4P can include both incentives and disincentives. Incentives relate to additional payments for meeting certain quality thresholds. Disincentives relate to withholding certain payments for not meeting those quality thresholds. An extension of the P4P concept relates to the implementation of the policy of nonreimbursable hospital-acquired conditions, formerly called “never events” by the Centers for Medicare and Medicaid. The Centers for Medicare and Medicaid has identified a list of hospital-acquired conditions, which are specific quality events that will result in no payment for care provided to patients (e.g., wrong site surgery, CA-BSI, and decubitus ulcers acquired in the hospital).

Quality reporting is also being used in a voluntary manner as a business growth strategy. Leading children’s hospitals across the United States actively compete to have high ratings in national quality evaluations that are reported in publications such as Parents (formerly Child) magazine and US News & World Report. Many children’s hospitals also have developed their own websites for voluntarily reporting their quality information for greater transparency. Although greater transparency may provide a competitive advantage to institutions, the underlying goal of transparency is to improve the quality of care being delivered, and for families to be able to make informed choices in selecting hospitals and physicians for their children.

Quality measures may also be used for purposes of certifying individual physicians as part of the MOC process. In the past, specialty and

<table>
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<tr>
<th>Table 2-3</th>
<th>Examples of National Pediatric Quality Measures</th>
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<tr>
<td><strong>NQF PEDIATRIC QUALITY INDICATORS</strong></td>
<td><strong>NQF-ENDORSED INPATIENT MEASURES AMONG PICUs</strong></td>
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<tr>
<td>Neonatal bloodstream infection rate</td>
<td>PICU standardized mortality ratio</td>
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<td>Transfusion reaction</td>
<td>PICU severity-adjusted length of stay</td>
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<td>PICU unplanned readmission rate</td>
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<tr>
<td>Gastroenteritis admission rate</td>
<td>Initiation and engagement of alcohol and other drug dependence treatment (IET)</td>
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<tr>
<td></td>
<td>Nursing hours per patient day</td>
</tr>
<tr>
<td></td>
<td>Preventive care and screening: screening for clinical depression and follow-up plan</td>
</tr>
<tr>
<td></td>
<td>Skill mix (RN, LVN/LPN, UAP, and contract)</td>
</tr>
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CAC, Children’s Asthma Care; CAHPS, Consumer Assessment of Healthcare Providers and Systems; ED, emergency department; HBIPS, hospital-based inpatient psychiatric services; LVN/LPN, licensed vocational/practical nurse; NHSN, National Healthcare Safety Network; NQF, National Quality Forum; PICU, pediatric intensive care unit; RACHS-1, risk adjustment for congenital heart surgery; RN, registered nurse; UAP, unlicensed assistive personnel.
subspecialty certification in medicine, including pediatrics, was largely based on demonstrating a core fund of knowledge by being successful in an examination. No specific evidence of competency in actual practice needed to be demonstrated beyond successful completion of a training program. There continues to be significant variations in practice patterns even among physicians who are board certified, which highlights the concept that medical knowledge is important, but not sufficient for the delivery of high-quality care. Subsequently, the American Board of Medical Specialties, including its member board, the American Board of Pediatrics, implemented the MOC process in 2010. Within the MOC process, there is a specific requirement (Part IV of MOC) for the physician to demonstrate the assessment of quality of care and implementation of improvement strategies as part of recertification in pediatrics and subspecialties. Lifelong learning and the translation of learning into practice are the basis for the MOC process and for an essential competency for physicians professionalism. There are also discussions to adopt a similar requirement for Maintenance of Licensure for physicians by state medical regulatory boards.

The Accreditation Council for Graduate Medical Education requires residency programs to incorporate QI curriculum to ensure that systems-based practice and QI are part of the overall competencies within accredited graduate medical training programs. One form of continuing medical education, the performance improvement continuing medical education, is used for ongoing physician education. These initiatives require physicians to measure the quality of care they deliver to their patients, to compare their performance to peers or known benchmarks, and to work toward improving their care by leveraging QI methods. This forms a feedback loop for continued learning and improvement in practice.

Prior to comparing quality measures data both within and across clinical settings, it is important to perform risk adjustment to the extent that is feasible. Risk adjustment is the statistical concept that utilizes measures of underlying severity or risk so that the outcomes can be compared in a meaningful manner. The importance of risk adjustment was highlighted in the PICU setting many years ago. The unadjusted mortality rate for large tertiary care centers was significantly higher than that for smaller hospital settings. By performing severity of illness risk adjustment it was subsequently shown that the risks in tertiary care large PICUs were higher because patients had higher levels of severity of illness. These patients were sicker than other patients, which would explain the higher mortality rate. Although this concept is now intuitive for most clinicians, the use of severity of illness models in this study allowed a mathematical estimate of patient severity using physiologic and laboratory data, which allowed for the statistical adjustment of outcomes. This permits meaningful comparisons of the outcomes of large and small critical care units. Severity of illness models and the concepts of statistical risk adjustment are most developed in pediatric critical care, but these concepts are relevant for all comparisons of outcomes in the hospital settings where sicker patients may be transferred to the larger institutions for care and, therefore, would be expected to have poorer outcomes as compared to other settings with less sick patients.

Risk adjustment can be performed at 3 levels. First, patients who are sicker can be excluded from the analysis, thereby allowing the comparisons to be within homogenous groups. Although this approach is relatively simple to use, it is limited in that it would result in patient groups being excluded from the analysis. Second, risk stratification can be performed using measures of patient acuity. An example of this relates to the use of the All-Patient Refined Diagnosis-Related Group system where patients can be grouped or stratified into different severity criteria based on acuity weights. This approach may provide relatively homogenous strata within which comparisons can be performed, but it is not able to predict the overall outcomes within patient risk groups. Third, severity of illness risk adjustment relates to the use of clinical data to predict the outcomes of patient groups. An example of a clinical severity of illness risk adjustment process is the use of the Pediatric Risk of Mortality (PRISM) scoring system in the PICU setting. The PRISM score, and its subsequent iterations, composed of a combination of physiologic and laboratory perimeters that are weighted on a statistical logistic scale to predict the risk of mortality within that PICU stay. By comparing the observed and expected outcomes (i.e., mortality or survival), a quantitative estimate of the performance of that PICU can be established which can then be used to compare outcomes with other PICUs (standardized mortality ratio).

Risk-adjustment systems have been effectively incorporated into specialty databases. An example of such a system is the Virtual Pediatric Intensive Care Unit System (VPS), which represents the pediatric critical care database system in the United States. The VPS, comprising more than 100 PICUs and cardiac PICUs across the United States, as well as international PICUs, currently has more than 300,000 patients within its database. The VPS database emphasizes data quality, both data validity and reliability, to ensure that the resulting data are accurate. Data validity has been established using standard data definitions with significant clinical input. Data reliability is established using interrater reliability to ensure that the manual data collection that involves several data collectors within pediatric institutions is consistent. The PRISM scoring system is programmed into the VPS software to allow the rapid estimation of the severity of illness of individual patients. This, in turn, allows risk adjustment of the various outcomes that are compared within institutions over time and across institutions for purposes of QI.

QUALITY AND PATIENT SAFETY

Safety is an important dimension of quality, and errors in healthcare are a leading cause of death and injury. Approximately 3–4% of hospitalized adult patients are harmed by the care that is supposed to help them, and 7% are exposed to a serious medication error that harms or could harm them. Multiple factors contribute to errors: an increasingly complex healthcare system with diffuse accountability; a culture of attributing errors to individuals, which overlooks problematic systems; lack of allegiance between physicians and hospitals, which detracts from patient-centered practices; and reimbursement policies that frequently discourage safety measures.

Medical Errors in Children’s Healthcare

Few epidemiologic data are available regarding medication errors in the pediatric setting, and the potential for pediatric inpatient medical errors is substantial. This may be partly a result of children having unique clinical experiences that are prone to error. These unique risk factors or safety issues, the “4 Ds,” are developmental change, dependence on adults, different disease epidemiology, and demographic characteristics. Developmental change might refer to the unique susceptibility of neonates to infections or the need for weight-based dosing with growth. Children’s dependence on adults puts them at heightened risk for experiencing medical errors because children do not usually manage their own treatments or provide their own medical history and may not have the insight to question their own care. Different disease epidemiology refers to the unique illnesses and medical needs that predispose children to unique safety events as compared with adults (e.g., birth trauma and screening for metabolic abnormalities). Children have distinct demographic characteristics and are more likely to live in poverty than any other segment of the population.

Adverse drug events (ADEs) may occur in pediatric patients at a similar rate as in adult patients; the potential ADE rate may be 3 times higher in children. A potential ADE is one that is intercepted before causing harm. Most potential ADEs occur at the stage of drug ordering and involve incorrect dosing, antineffective drugs, and intravenous medications. In an ambulatory setting, 13% of prescriptions for children might refer to the unique susceptibility of neonates to infections or the need for weight-based dosing with growth. Children’s dependence on adults puts them at heightened risk for experiencing medical errors because children do not usually manage their own treatments or provide their own medical history and may not have the insight to question their own care. Different disease epidemiology refers to the unique illnesses and medical needs that predispose children to unique safety events as compared with adults (e.g., birth trauma and screening for metabolic abnormalities). Children have distinct demographic characteristics and are more likely to live in poverty than any other segment of the population.
Key Issues in Patient Safety

Making care safer requires the identification and control of things that could cause harm to patients. Several key concepts regarding patient safety are summarized in the following sections and are available in curriculum overviews at [www.patientsafety.gov](http://www.patientsafety.gov), [www.npsf.org](http://www.npsf.org), and [www.va.gov](http://www.va.gov).

Systems Approach

The majority of healthcare errors result from faults intrinsic to the processes by which healthcare is delivered, rather than individual mistakes. This systems approach compels organizations to respond to adverse events not by blaming individuals, but by improving the conditions under which individuals work. An error is viewed as a symptom of trouble in a process that offers an opportunity for improvement and the potential to implement safeguards.

Developing a Culture of Safety

The biggest challenge in making the health system safer is changing the culture from one of treating errors as personal failures to one of treating errors as opportunities to improve the system. Organizations need to foster a culture of learning in which each individual will feel accountable for ensuring a safe and quality program, communication is open, and teamwork is valued. Reporting of errors should be valued, reports of adverse events should be handled confidentially, and those who report errors should be protected from discovery. Developing a culture of learning involves the compassionate and appropriate disclosure of system failures and medical errors to patients and families. It has also been shown that utilizing multiple approaches to identify adverse events may be effective.

Communication

Good communication among the healthcare team is essential for patient safety. Healthcare involves the safe transfer of responsibility for patient care and the transfer of patient information. Poor communication or miscommunication creates the opportunity for incorrect or incomplete transfer of vital information during the transfer of responsibility for patient care from one provider to another, thus placing the patient at risk for serious medical error. The potential for harm is increased when the healthcare team and the patient do not share a native language. Errors in medical interpretation are common, with omissions being the most frequent. Ad hoc interpreters are significantly more likely to commit errors with harmful clinical consequences than are hospital interpreters.

Teamwork and Authority Gradients

Ensuring a systems approach to healthcare safety involves a paradigm shift. Healthcare has tended to be a hierarchical endeavor, with physicians in leadership roles that allowed significant amounts of autonomy. This authority gradient can predispose to communication failures: junior team members may be hesitant to speak up and senior members may resist feedback. A medical student or nursing assistant may be hesitant to inform an attending physician of a potential error. In a culture of safety, team members with different positions of authority must interact to facilitate optimal patient care; all are empowered to voice a safety concern. The composition of the teams may vary day to day because of shifting schedules. Senior leaders must be able to engender trust rapidly among team members, accept that human error is inevitable, and encourage behaviors that prevent or mitigate the harm that results from errors. Healthcare can learn important lessons for safety from industry. Experiences from industries that have standardized and achieved a high level of safety and reliability (e.g., the airline and nuclear industries) can help inform future healthcare systems in both proactive (addressing complex areas of healthcare before implementing an intervention) or reactive (reviewing reports of “close calls” or injuries). Computerized physician order entry, an example of HFE in healthcare, has been shown to decrease the rate of medication errors in pediatric inpatient settings.

The role of a team based approach along with the need to consider human factors requires the creation of systems that are designed to improve outcomes. Recent studies from the nursing literature have identified the positive impact of continuity of nursing care on patient outcomes in high-risk settings, and also the potential detrimental impact on patient outcomes with unduly long nursing shifts in the inpatient acute care setting for children.

Reliability

Reliability in healthcare is defined as the measurable capability of a process, procedure, or health service to perform its intended function in the required time under commonly occurring conditions (i.e., providing intended care on a consistent basis). Most healthcare organizations currently perform at Level 1 reliability, which means that processes are performed with only an 80-90% success rate. To achieve Level 2 performance (≤5 failures/100 opportunities), processes must be intentionally designed with tools and concepts based on the principles of HFE. Performance at Level 3 (≤5 failures/1,000 opportunities), requires a well-designed system with low variation and cooperative relationships and a state of what has been called “mindfulness,” where attention is paid to processes, structure, and their relationship to outcomes. Cincinnati Children’s Hospital Medical Center used reliability science and the Model for Improvement to institute a ventilator-associated pneumonia protocol that led to an 87% reduction in ventilator-associated pneumonias per 1,000 ventilator days (from a fiscal year average of 7.5 to an average of only 0.95).

Such efforts are now expanding from individual institutions to the regional level. The Solutions for Patient Safety is a new collaboration of multiple pediatric institutions at a state level to share quality and safety data in a transparent manner, and to create a culture of shared learning.

IMPACTS OF THE U.S. HEALTHCARE REFORM FOR QUALITY

In 2010, the Affordable Care Act was enacted into law. This significant health care legislation attempting to achieve the vision of universal health care includes an emphasis on access to health care, the implementation of consumer protections (e.g., preexisting conditions), and improving quality and lowering the cost of health care.

Regarding quality and safety in health care for children, health care reform has three key implications. First, universal coverage optimizes access and includes expanding coverage for young adults to age 26 yr. Second, various initiatives related to quality, safety, patient-centered outcomes research, and innovation were implemented and funded. For example, the Agency for Healthcare Research and Quality (AHRQ) has funded a national effort to establish seven centers of excellence through the Pediatric Quality Measurement Program (PQMP) to improve existing pediatric quality measures and create new measures that can be used by states and in a variety of other settings to evaluate quality of care for children. Third, a paradigm shift in the existing model of health care delivery system has been vertically integrated toward a model of horizontal integration. This has led to the creation and rapid growth of integrated delivery systems and risk-sharing relationships of accountable care organizations (ACOs).

Accomplishing this strategic direction is resulting in three new areas of rapid growth in the quality arena. “Big Data” relates to the notion of linking potentially disparate sources of data to generate new knowledge, accelerate innovation, and improve outcomes. Big Data is unique in that it aims to link structured and unstructured data sources, including data emerging from databases, registries, clinical records, and social media. A key strength of using a large volume of data across multiple sources by linking it to create Big Data is a significant increase in power for early prediction and new knowledge generation that can be rapidly implemented.

Another area of increasing emphasis is the notion of population health. This is important because it expands the traditional role of
physicians to improve quality of care for individual patients to also improve the quality of care for larger populations. Populations can be defined by geographic constraints or disease/patient condition. The notion of population health is integral for achieving the “triple aim” vision of quality of care. Efforts to link payment and reimbursement for care delivery by physicians and health systems are being increasingly tied to measurable improvements in population health. To achieve a meaningful improvement in population outcome, physician practices will need to embrace the emerging paradigm of practice transformation. Practice transformation has many facets, including the adoption of a “medical home,” the seamless connectivity across the primary care and subspecialty continuum, and a strong connection between the medical and social determinants of health care delivery. To implement successful practice transformation, hospitals are increasingly adopting a broader view to evolve into health care systems that serve children across the entire range of the care continuum, including preventive and primary care, acute hospital care, and partnerships with community organizations for enhancing the social support structure. In addition, new risk-sharing payment models are evolving, resulting in the growth of entities such as ACOs, which represent a financial risk-sharing model across primary and subspecialty care and hospitals, resulting in an unprecedented level of health care integration to improve quality of care.

THE EVOLUTION OF QUALITY TO OUTCOMES TO VALUE

Most efforts at QI tend to emphasize enhancements in the process of healthcare delivery with the assumption that this will lead to improvements in outcomes. With the growing adoption of electronic health records that can allow tracking patients across the continuum of care, it will be possible to measure outcomes. Efforts at quality and outcomes must move toward creating value from the perspective of patients and families. Healthcare delivery systems must be developed based upon patient needs. Healthcare providers should lead this initiative to create value and that outcomes being measured should matter to patients.

INFORMATION TECHNOLOGY AND QUALITY IMPROVEMENT

The underlying goal of the HIT movement is to improve quality and safety. HIT includes electronic health records, personal health records, and health information exchange. The purpose of a well-functioning electronic health record is to allow collection and storage of patient data in an electronic form, to allow this information to be provided to clinicians and healthcare providers, to have the ability to allow clinicians to enter patient care orders through the computerized physician order entry, and to have the infrastructure to provide clinical decision support which will improve physician decision making at the level of individual patients. Personal health records will allow patients and families to be more actively engaged in managing their own health by monitoring their clinical progress and laboratory information, and also be able to communicate with their physicians for appointments, obtaining medications, and getting their questions answered. Appropriate, timely, and seamless sharing of patient information across physician networks and healthcare organizations is critical to quality care and to achieve the full vision of a medical home for children. Health information exchange would allow the sharing of healthcare information in an electronic format to facilitate the appropriate connections between providers and healthcare organizations within a community or region. However, significant cost and time barriers remain for adoption of HIT. The entire field of HIT as a mechanism to improve quality is likely to continue to be in the forefront of the quality journey for physicians and healthcare organizations for the next several years.

Despite the emphasis on HIT and data, it is important to understand that data does not lead to improvement in itself. Improvement is an affirmative choice and requires translating data (measurement) into clinically relevant information (data that has context and relevance) that is actionable for QI.

QUALITY IMPROVEMENT OR RESEARCH?

Research aims at generating new knowledge. QI aims at implementing the new knowledge into practice. Whereas research aims at developing new generalizable knowledge, QI aims at adopting the available evidence into practice at a local level. With the growing interest in research in the field of QI and efforts to expand the generalizability of QI initiatives, there can be situations in which research and QI overlap. In the future, the gap between QI and research will likely narrow to allow a continuum of active knowledge transfer from research into practice using QI methods.

EXPANDING INDIVIDUAL QUALITY IMPROVEMENT INITIATIVES TO SCALE

Despite the success of individual QI and patient safety projects, the overall progress to achieve large-scale improvements to reach all children across the spectrum of geographic location and socioeconomic status remains limited. This contributes to the health disparities that persist for children with significant differences in access and quality of care. A potential factor that limits the full impact of QI is the lack of strategic alignment of improvement efforts with hospitals, health systems, and across states.

This challenge can be viewed from a system standpoint in being able to conduct and expand QI from a micro level (individual projects), to the meso level (regional), to the macro level (national and international). The learning from individual QI projects for addressing specific challenges can be expanded to the regional level by ensuring that there is optimal leadership, opportunity for education, and adoption of improvement science (Fig. 2-10). To further expand the learning to a national and international level, it is important to leverage implementation science to allow a strategic approach to identification of the key success ingredients to expand the improvement strategy. To fully leverage the synergies to impact the quality of care delivered to children, it is important for national and international healthcare organizations to effectively collaborate from a knowledge management and improvement standpoint (Table 2-4).

INTERNATIONAL EFFORTS FOR QUALITY IMPROVEMENT

The implications of QI for healthcare delivery systems are equally relevant to international venues as to the United States. Many developing and industrialized countries are in the process of expanding their pediatric care delivery systems to have a greater presence of tertiary and quaternary care delivery. The understanding and adoption of QI principles during the early phase of expansion will result in the efficient use of resources with the greatest potential for favorably impacting health outcomes in children. Pediatric clinical practices in many developing countries have already adopted several unique, innovative approaches to allow delivery and creation of healthcare systems despite limited resources. These local innovations need to be expanded to allow for learning across countries. QI provides a unique strategy that can result in linking of a global community for the care of children including real-time learning and sharing of innovative best practices.
across the developing and industrialized worlds. Many international efforts to improve QI are already in progress. For example, the World Health Organization (WHO) has highlighted the global progress in adoption of HIT in many countries. A survey performed by WHO between 2005 and 2006 identified that nearly half of 112 countries responding to the survey already have national task forces or related groups to provide the national direction for e-health strategies. Pediatricians have the unique opportunity to provide leadership to evolving governmental-private-public partnerships in designing the next generation of pediatric healthcare delivery systems.

Bibliography is available at Expert Consult.
Pediatric ethics is the branch of bioethics that analyzes moral aspects of decisions made relating to the healthcare of children. In general terms, the autonomy-driven framework of adult medical ethics is replaced by a beneficent paternalism (or parentalism) in pediatrics. Pediatric ethics is distinctive because the pediatric clinician has an independent fiduciary obligation to act in a younger child’s best interest that takes moral precedence over the wishes of the child’s parent(s). For older children, the concept of assent suggests that the voice of the patient must be heard. These factors create the possibility of conflict among child, parent, and clinician. The approach to the ethical issues that arise in pediatric practice must include respect for parental responsibility and authority balanced with a child’s developing capacity and autonomy. Heterogeneity of social, cultural, and religious views about the role of children adds complexity.

ASSENT AND PARENTAL PERMISSION

The doctrine of informed consent has limited direct application to children and adolescents who lack decisional capacity. The capacity for informed decision making in healthcare involves the ability to understand and communicate, to reason and deliberate, and to analyze conflicting elements of a decision using a set of personal values. The age at which a competent patient may legally exercise voluntary and informed consent for medical care varies from state to state and may be limited to specific conditions (sexually transmitted infections, family planning, drug or alcohol abuse).

In contrast to decisions about one’s own care, a parent’s right to direct a child’s medical care is more limited. For this reason, the term parental consent is misleading. The concept of parental permission (rather than consent) reflects a surrogate or proxy decision made by a parent on behalf of a child. It is constrained both by the child’s best interest and the independent obligation of clinicians to act in the child’s best interest, even if this places them in conflict with a parent. In any given instance, the decision of what is or is not in a child’s best interest may be difficult, especially given the diverse views of acceptable child rearing and child welfare. Parents are (and should be) granted wide discretion in raising their children. In cases involving a substantial risk of harm, the moral focus should be on avoiding or preventing harm to the child, not on a parental right to decide. While the term “best” interests may be too high of a threshold requirement, a minimum standard of “basic” interests is ethically obligatory.

Respect for children must account for both a child’s vulnerability and developing capacity. This respect encompasses both the protective role of parental permission and the developmental role of child assent (the child’s affirmative agreement). Understanding the concept of assent is one of the major conceptual challenges in pediatric ethics. The dissent (or disagreement) of a child is the opposite of assent and is also morally relevant. Pediatric ethics requires clinicians and parents to override a child’s dissent when a proposed intervention is essential to the child’s welfare. Otherwise, assent should be solicited and dissent should be honored. In seeking younger children’s assent, a clinician should help them understand their condition, tell them what they can expect, assess their understanding and whether they feel pressured to assent, and solicit their willingness to participate. All efforts must be made to delineate situations in which the test or procedure will be done regardless of the child’s assent/dissent, and in such cases the charade
of soliciting assent should be avoided. There is an important distinction between soliciting assent and respectfully informing a child that a test or procedure will take place regardless of the child’s decision. Optimally, an educational process can transpire (if time allows) to gain the trust and assent of the child-patient. When this cannot occur, pediatric ethics requires that clinicians apologize to a child for acting to override dissent.

Older children or adolescents may have the cognitive and emotional capacity to fully participate in healthcare decisions. If so, the adolescent should be provided with the same information as would be given to an adult patient. In cases like this, the patient may be able to provide informed consent ethically but not legally. The adolescent’s parent(s) remain in a guiding and protective role. The process of communication and negotiation will be more complex should disagreement arise between the parent and adolescent.

**TREATMENT OF CRITICALLY ILL CHILDREN**

Infants, children, and adolescents who become critically ill may recover fully, may die, or may survive with new or worsened limitations of function. Uncertainty about outcomes can make planning goals of care difficult, or if misunderstandings between patient, families, and medical staff occur, may drive conflict over treatment proposals. Ethical issues that arise during critical illness include balancing benefits, burdens, and harms of therapy in the face of uncertainty; maintaining a helpful degree of transparency and communication about medical standards of care at an institution; understanding and respecting religious and cultural differences that impact requests for or refusal of treatments; defining limits of therapy based on assessments of medical futility; recognizing the moral equivalence of not starting an ineffective treatment and stopping (although the 2 acts may feel very different to families and providers); and controversies such as withholding medically administered nutrition and hydration.

**Transiting the Goals of Care**

Most acutely ill children who die in an ICU do so after a decision has been made to either forgo or withdraw life-sustaining medical treatment (LSMT), and the same may apply in the chronically ill population. LSMT is justified when the anticipated benefit outweighs the burdens to the patient; the availability of technology does not in and of itself obligate its use. Decisions to use, limit, or withdraw LSMT should be made after careful consideration of all pertinent factors recognizable by both family and medical staff, including medical likelihood of particular outcomes, burdens on the patient and family, religious and cultural decision-making frameworks, and input by the patient when possible. Although fear of legal repercussions may sometimes drive treatment and medical advice, ultimate decisions should be based on what is thought to be best for the patient rather than based on fears of litigation.

The concept of futility has been used to support unilateral forgoing of LSMT against the wishes of patients and families by holding that clinicians should not provide futile (or useless) interventions. If medical futility is defined narrowly as the impossibility of achieving a desired physiologic outcome, then forgoing a particular intervention is ethically justified. However, this approach may not adequately engage professionals and families in understanding facts and values that might allow the same therapy to reach other goals, and may leave medical and family stakeholders in permanent conflict. If agreement cannot be reached through clear and compassionate communication efforts, further input can be sought from an ethics consultant or committee.

**Communication**

About life-threatening or life-altering illness is challenging, and requires skills learned through both modeling and practice. These skills include choosing a setting conducive to what may become 1 or more long conversations; listening carefully to children’s and families’ hopes, fears, understanding, and expectations; explaining medical information and uncertainties simply and clearly without complicated terms and concepts; conveying concern and openness to discussion; and being willing to share the burdens of decision-making with families by giving clear recommendations. Discussing difficult topics with children requires an understanding of child development, and can be aided by professionals such as child psychologists or child life specialists. Such conversations and their outcomes have a major impact on the future care of the patient, on families, and on medical staff. For this reason, ongoing evaluation of goals and communication about them is needed with families and within complex medical teams as the course of the illness unfolds.

Experts recognize that good medical care involves providing for communication, symptom management, and a range of supportive services from the onset of acute illness. In this way, if an illness proves to be life-limiting in spite of aggressive therapies, the elements of palliative care are already in place. This concept has had difficulty gaining traction, especially in critical care settings, because of the mistaken conflation of broadly defined palliative measures with hospice care. Palliative care interventions focus on the relief of symptoms and conditions that may detract from quality of life regardless of the impact on a child’s underlying disease process, and as such are important whether care is focused on cure or on transitioning to end-of-life care (see Chapter 43). Some interventions regarded as life-sustaining, such as chemotherapy, may be ethically acceptable in the end-of-life setting if their use decreases pain and suffering rather than results only in prolonging death.

**Withholding and Withdrawing Life-Sustaining Treatment**

Limitation of interventions or withdrawal of existing therapies are ethically acceptable if they are congruent with a plan of care focused on comfort and improved quality at the end of life rather than cure. The prevailing view in Western, traditional medical ethics is that there is no moral distinction between withholding or withdrawing interventions that are not medically indicated. Uncertainty in predicting a child’s response to treatment may drive the initiation and continuation of interventions that are no longer supportive of shared goals of care. It is necessary to continually evaluate the results of these treatments and the evolution of the illness to recognize whether such interventions continue to be the best medical and moral choices. Maintaining the focus on the child rather than on the interests of parents or medical staff will help guide decision making.

The decision about whether or not to attempt cardiopulmonary resuscitation may become an issue to discuss with parents of children living with life-threatening or terminal conditions. All elements of end-of-life care approaches, including resuscitation status, should be supportive of agreed-on goals of care. It is imperative that decisions and plans are effectively communicated to all caregivers in order to avoid denying medically effective interventions and measures to ensure comfort. Orders about resuscitation status should clarify the plan regarding intubation and mechanical ventilation, the use of cardiac medications, chest compressions, and cardiovascular. Because goals of care may change over time, a medical order regarding resuscitation is not irrevocable. Clinicians may assume that the absence of a do-not-attempt-resuscitation (DNAR) order obligates them to perform a prolonged resuscitation. This action may not be ethically supportable if resuscitative efforts will not achieve the desired physiologic endpoint. In all cases, treatments should be tailored to the child’s clinical condition, balancing benefits and burdens to the patient. Resuscitation should not be performed solely to mollify parental distress at the tragic time of the loss of their child.

**Advance Directives.** An advance directive (AD) is a mechanism that allows patients and/or appropriate surrogates to designate the desired medical interventions under applicable circumstances. Discussion and clarification of resuscitation status should be included in advance care planning, and for children attending school in spite of advanced illness, may need to be addressed in that setting. Decisions regarding resuscitation status in the out-of-hospital setting can be an important component of providing comprehensive care.

The 1991 federal Patient Self-Determination Act requires that healthcare institutions ask adult (>18 yr) patients whether they have completed an AD and, if not, inform them of their right to do so. Few states support creation of broad ADs for minors because ADs are
traditionally created by persons with legal decision-making capacity, but some have moved in this direction because it is recognized that minors may be capable of participating in decision making, especially if they have been dealing with chronic disease. However, surrogate decision makers may participate in advance care planning for their children. Most states have approved the implementation of prehospital or portable DNAR orders, through which adults may indicate their desire not to be resuscitated by emergency personnel. On a state-by-state basis, portable orders regarding resuscitation status may also apply to children. If DNAR orders exist for an infant or a child, it is important to communicate effectively about their intent among all potential caregivers, because nonmedical stakeholders such as teachers or sitters may not wish to be in the position of interpreting or honoring them. Some institutions have established local policies and procedures by which an appropriately executed outpatient DNAR order can be honored upon a child's arrival in the emergency department. Key features may include a standardized document format, review by an attending physician, ongoing education, and involvement of a pediatric palliative medicine service.

In cases involving prenatal diagnosis of a lethal or significantly burdensome anomaly, parents may choose to carry their fetus/unborn child to term in order to cherish a short time with the infant after birth, but do not feel that resuscitation or certain other aggressive measures would support their well-considered goals of care. In this setting, a birth plan explaining the reasons for each choice can be developed by the parents and medical staff prior to delivery and shared with involved medical staff. This approach gives staff a chance to find other caregivers if they are uncomfortable with the approach, without abandoning the care of the child. If, after evaluation at birth, the infant's condition is as had been expected, honoring the requested plan is ethically supportable and should be done in a way that optimizes comfort of the infant and family.

Many states utilize Physician Orders for Life-Sustaining Treatment or Medical Orders for Life-Sustaining Treatment approaches to communicating a patient or surrogates wishes regarding advance care planning. It is important for pediatricians to learn which pathways for communicating goals of care are available in their own states.

**Artificial Hydration and Nutrition.** Issues surrounding withholding or withdrawing artificial hydration and nutrition are controversial, and interpretations are affected by parental, religious, and medical beliefs. Any adult or child who is fully dependent on the care of others will die as a result of not receiving hydration and nutrition. Case law has supported the withholding of artificially administered nutrition and hydration in the setting of adult vegetative or permanently unconscious patients who can be shown to have previously expressed a wish not to be maintained in such a state. This requires a valid AD, or for a surrogate decision maker to speak on behalf of the patient’s known wishes. Because infants and many children have not reached a developmental stage in which such discussions would have been possible, decisions about stopping artificially administered nutrition and hydration as a limitation of treatment are more problematic. These decisions should be based on what families and caregivers decide best support comfort. In the child who is imminently dying, unaware of hunger, does not tolerate enteral feedings, and in whom family and staff agree that IV nutrition and hydration only prolong the dying process, it may be ethically supportable to withhold or withdraw these treatments based on a benefit–burden analysis.

**The Doctrine of Double Effect.** Treatment decisions at the end of life may include limitations of certain LSMT, or may involve the use of analgesic or sedative medications that some fear may shorten life, thereby causing death. The doctrine of double effect holds that an action with both good and bad effects is morally justifiable if the good effect is the only one intended, and the bad effect is foreseen and accepted, but not desired. In pediatrics, it is most commonly applied in end-of-life cases, when upward titration of medication (opiates) necessary to relieve pain, anxiety, or air hunger can be expected to result in a degree of respiratory depression. In such cases, meeting a provider’s obligation to relieve suffering is the intended effect, and this obligation to the patient outweighs the acknowledged but unavoidable side effect. Choosing medications that adequately relieve symptoms with minimal adverse effects would be ethically preferable, but the obligation to provide comfort at the end of life outweighs the foreseeable occurrence of unavoidable side effects. Hastening death as a primary intention is not considered to be morally acceptable.

Providing pain medication guided by the doctrine of double effect should not be confused with active euthanasia. The distinction is clear:

- In active euthanasia, causing death is chosen as a means of relieving the symptoms that cause suffering.
- Under the doctrine of double effect, adequate management of pain, anxiety, or air hunger is recognized as an obligation to dying patients, and is provided by careful titration of medications in response to symptoms. If death occurs sooner as a result, this is accepted.

In both cases the patient dies and in both cases suffering ends, but immediate death is the intended consequence only in the case of euthanasia. Codes of ethics and legislation in many states support the obligation to provide pain and symptom relief at the end of life, even if this requires increasing doses of medication.

**CARE OF DISABLED NEWBORNS**

In 1982, an infant with Down syndrome and esophageal atresia was allowed to die at 6 days of age at the parents’ request. Prior to this case becoming public, prevailing opinion was that withholding aggressive treatments from infants who were predicted to be significantly disabled from conditions such as Down syndrome or meningomyelocele was ethically acceptable, and was being done on advice of physicians who felt that they and families should be able to decide what was best for an individual infant. The public legal controversy resulted in federal legislation called the “Baby Doe Regulations,” prohibiting the withholding of medically beneficial treatment from disabled infants except under conditions of permanent unconsciousness, “futile” treatment, and “virtually futile” treatment that imposes excessive burdens on the infant. Today, treatment options and potential outcomes have improved, attitudes toward and social supports for disabled children have evolved, and initial aggressive treatment of infants with severe disabilities has become more common. Studies done since the Baby Doe Regulations went into effect indicate that most pediatricians supported parental rather than government control of such decisions, and felt that they were now constrained to institute treatments that served neither patients nor families well.

One consequence of the legislation was a shift from potential undertreatment to widespread overtreatment (LSMT that does not serve the interests of the child) of severely disabled newborns. The legislation has been difficult to enforce, and subsequent case law has upheld the right of a parent to decide to forgo LSMT in certain instances. The 2002 “Born Alive Act” defined a human being as any infant born alive at any stage of development. It has been thought by some to pose a risk to the ethical practice of providing palliative care for newborns, though many believe that no changes in patient management are necessary.

Active euthanasia of severely suffering disabled newborns has been legalized in the Netherlands, using a protocol designed to minimize risk of abuse and maximize transparency. Although there may be some controversy over the subject in the United States, there is consensus that active euthanasia is not ethically acceptable in the care of infants and children.

**DECLARING DEATH AND ORGAN DONATION**

Donation of solid organs necessary to support life can occur after a patient is declared dead based on either irreversible cessation of neurologic function of the brain and brainstem (death by neurologic criteria, or “brain death”) or a predetermined period of cardiac asystole called “circulatory death.” To avoid a potential conflict of interest by surgeons or others caring for a potential organ recipient, the request for organ donation should be separated from the clinical discussion of either brain death or withdrawal of LSMT. Although clinicians may be
the first providers to enter discussion about death and organ donation with family members during conversations about outcomes and options, detailed discussion of organ donation should be done by other individuals who are specifically trained for this purpose. This “decoupling” of clinical decision making from a request for organ donation by trained individuals, perhaps by providing families with expert information without a perceived conflict of interest, has been associated with improved donation rates.

**Death by Neurologic Criteria**

**Death by neurologic criteria (DBNC),** commonly referred to as brain death, may be difficult for families to understand when the child appears to be breathing (albeit on a ventilator), pink, and warm to the touch, and when language such as life support is used at the bedside by staff. Studies also document clinician misunderstanding of the diagnosis of DBNC. For these reasons, strict criteria adhering to nationally accepted guidelines must be used to determine when irreversible cessation of brain and brainstem function has occurred, and to adequately document these findings (see Chapter 68.1).

The states of New York and New Jersey allow families to object on religious grounds to the declaration of DBNC. In that situation, the clinical determination of the DBNC sets the stage for a discussion of forgoing LSMT, rather than the death of the patient. A unilateral decision not to initiate new or escalate existing interventions is ethically supportable under these circumstances, given the documented death of the patient. Even though it would seem to follow that a similar unilateral decision to withdraw existing interventions would also be supportable, this act is not in accordance with the intent of the state laws. Institutional procedures for conflict resolution, including involvement of the courts if necessary, should be followed.

**Circulatory Death**

Protocols allowing for organ donation after determination of circulatory death (DDCD) rather than after DBNC have been developed. DDCD can occur under either controlled (after planned withdrawal of LSMT) or uncontrolled (after failed CPR) circumstances, but in both cases require rapid removal of organs in order for subsequent transplantation to be successful. An increasing number of programs are pursuing DDCD protocols after federal legislation began requiring accredited hospitals to address the issue in hopes of decreasing organ shortages. Hospitals can make policy that either allows or disallows the process. In adults, consent for donation by either means can be obtained from patients or surrogates; for children, parents or guardians would make the decision to donate.

Ethical concerns about DDCD protocols focus on two principles that have served as the basis for organ donation: (1) the “dead donor rule” limiting the donation of vital organs to those who are irreversibly dead (either by circulatory or neurologic criteria, not both), and (2) the absence of conflict of interest between clinical care and organ procurement. With DDCD protocols, irreversibility has been declared at varying times after asystole occurs (usually 2-5 min), to avoid spontaneous return of circulation after forgoing CPR. To avoid a potential conflict of interest during the DDCD process, there is a requirement for strict decoupling of end-of-life care after discontinuation of LSMT and presence of the transplant team. Unlike in the setting of DBNC, a patient who is being considered for DDCD remains alive until after asystole has occurred. Careful evaluation by the transplantation team and organ procurement agency is performed before discontinuation of LSMT. Then, in most DDCD protocols the medical caregivers from the ICU continue to care for the patient until after death by cardiac criteria has been declared, and only then is the surgical transplant team allowed into the room to procure organs.

It is **ethically imperative** to correctly diagnose the state of death, whether by neurologic criteria or prior to organ donation after cardiac death. Doing so avoids the danger of removing life-sustaining organs from a living person. Strict adherence to an ethically sound protocol is the best way to prevent both the perception and the potential reality of mistakes related to the pronunciation of death and organ procurement.

**RELIGIOUS OR CULTURAL OBJECTIONS TO TREATMENT**

Differences in religious beliefs or ethic-based cultural norms may lead to conflict between patients, families, and medical caregivers over the approach to medical care. Pediatricians need to remain sensitive to and maintain an attitude of respect for these differences, yet recognize that an independent obligation exists to provide effective medical treatment to the child. An adult with decision-making capacity is recognized as having the right to refuse treatment on religious or cultural grounds, but children who have not yet developed this capacity are considered a vulnerable population that has a right to treatment. In situations that threaten the life of the child or that may result in substantial harm, legal intervention should be sought if reasonable efforts toward collaborative decision making are ineffective. If a child’s life is imminently threatened, medical intervention is ethically justified despite parental objections.

**PEDIATRIC ETHICS COMMITTEES AND ETHICS CONSULTATION**

Most hospitals have institutional ethics committees to assist with policy development, education, and case consultation. When these committees serve institutions caring for children, they may be referred to as pediatric ethics committees. Because of the important differences in approach between adult and pediatric ethics, member expertise on this committee should include those with special insight into the unique ethical issues arising in the care of children. Such committees generally provide ethics consultation advice without mandating action or being determinative. For the vast majority of decisions involving the medical treatment of children (including forgoing LSMT), pediatric clinicians and parents are in agreement about the desirability of the proposed intervention. Because of the ethical importance of assent, the views of older children should also be given considerable weight.

Pediatric ethics committees typically perform at least 3 different functions: (1) the drafting and review of institutional policy on such issues as DNAR orders and forgoing LSMT; (2) the education of healthcare professionals, patients, and families about ethical issues in healthcare; and (3) case consultation and conflict resolution. Although the process of case consultation may vary, ideally the committee (or consultant) should adopt a collaborative approach that uncovers all the readily available and relevant facts, takes into account the values of those involved, and balances the relevant interests, while arriving at a recommendation based on a consistent ethical analysis. One helpful approach involves consideration of the 4 following elements: (1) medical indications, (2) patient preferences, (3) quality of life, and (4) contextual features. Another framework based on principles would suggest attention to respect for persons, beneficence/nonmaleficence, and justice. Pediatric ethics committees often play a constructive role when parents and medical staff cannot agree on the proper course of action. Over the past several decades, these committees have acquired considerable influence and are increasingly recognized by state courts as an important aid in decision making. The membership, policies, and procedures of a pediatric ethics committee should conform to accepted professional standards.

**NEWBORN SCREENING AND GENETIC TESTING**

The *Oxford Dictionary of Public Health* defines **screening** as “the identification of a previously unrecognized disease or disease precursor, using procedures or tests that can be conducted rapidly and economically on large numbers of people with the aim of sorting them into those who may have the condition(s)...and those who are free from evidence of the condition(s).” Several programs, such as newborn screening for inborn errors of metabolism (see Chapter 84; e.g., phenylketonuria and hypothyroidism), are rightly counted among the triumphs of contemporary pediatrics. The success of such programs sometimes obscures serious ethical issues that continue to arise in proposals to screen for other conditions for which the benefits, risks, and costs have not been clearly established. Advances in genetics and technology have led to exponential growth in the number of conditions
for which screening programs might be considered, with insufficient opportunity to study each proposed testing program (see Chapter 78).

The introduction of screening efforts should be done in a carefully controlled manner that allows for the evaluation of the costs (financial, medical, and psychologic) and benefits of screening, including the effectiveness of follow-up and treatment protocols. New programs should be considered experimental until the risks and benefits can be carefully evaluated. Screening tests that identify candidates for treatment need to have demonstrated sensitivity, specificity, and high predictive value, lest individuals be falsely labeled and subject to possibly toxic treatments or to psychosocial risks. As newborn screening tests are being developed, parents should be given the opportunity to exercise informed parental permission or refusal. However, once a particular screening test has been clearly demonstrated to benefit the individual or public health, a formal, active parental permission process may not be ethically obligatory.

A persistent ethical issue is whether screening should be (1) voluntary (“opt in”), (2) routine, with the ability to “opt out” or refuse, or (3) mandatory. A voluntary approach entails an informed decision by parents before screening. Concern is often expressed that seeking parental permission is ethically misguided for tests of clear benefit, such as phenylketonuria screening, because refusal would constitute neglect. Routine testing with an opt-out approach requires an explicit refusal of screening by parents who object to this intervention. The principal ethical justification for mandatory screening is the claim that society’s obligation to promote child welfare through early detection and treatment of selected conditions supersedes any parental right to refuse this simple and low-risk medical intervention. Parental permission is clearly required when there is a research agenda (i.e., for incorporating experimental tests into established screening programs).

Genetic testing of young children for late-onset disorders such as the BRCA1 and BRCA2 breast cancer risk genes has been the subject of some ethical controversy. Knowledge of increased risk status may lead to lifestyle changes that can reduce morbidity and the risk of mortality, or may precipitate adverse emotional and psychologic responses and discrimination. Because many adults choose not to be tested for late-onset disorders, one cannot assume that a child would want or will benefit from similar testing. Genetic testing of young children for late-onset disorders is generally inappropriate unless such testing will result in interventions that have been shown to reduce morbidity and mortality when initiated in childhood. Otherwise, such testing should be deferred until the child has the capacity to make an informed and voluntary choice. This ethical approach is founded on the work of philosopher Joel Feinberg’s writing on the “child’s right to an open future.”

ADOLESCENT HEALTHCARE

Adolescent Assent and Consent

Many adolescents are more like adults than children in their capacity to understand healthcare issues and to relate them to their life goals (see Chapter 110). Teenagers may lack legally defined competency, yet they may have developed the capacity to meet the elements of informed consent for many aspects of medical care (see Chapter 112). There are also public health reasons for allowing adolescents to consent to their own healthcare with regard to reproductive decisions, such as contraception, abortion, and treatment of sexually transmitted infections. Strict requirements for parental permission may deter adolescents from seeking healthcare, with serious implications for their health and other community interests.

Counterbalancing these arguments are legitimate parental interests to maintain responsibility and authority for child rearing, including the opportunity to influence the sexual attitudes and practices of their children. Others claim that access to treatment such as contraception, abortion, or needle exchange programs implicitly endorses sexual activity or drug use during adolescence. Pediatricians should not impose their own moral beliefs in these disputes. Rather, they should provide unbiased evidence-based information and nonjudgmental support. One guiding principle should be encouragement of children and adolescents to begin taking responsibility, with guidance, for their own health. This requires some input from parents or guardians but also some privacy during decision making as they achieve developmentally anticipated separation from parental control.

Chronic Illness

The normal process of adolescent development involves gradually separating from parents, establishing self-confidence, asserting individuality, developing strong peer relationships, solidifying an ability to function independently outside the family, and taking on increasing autonomy in healthcare decisions. Most developmentally normal children older than age 14 yr understand the implications of well-explained medical options as well as the average adult, and their input into their own care should be respected. For children living with chronic illness, the ability to make medical decisions for themselves may either occur earlier than for those who have been previously healthy, or may occur later if, because of illness, they have not been able to achieve normal developmental milestones or psychological maturity. The clinician’s role involves assessment of the individual adolescent patient’s ability to understand the medical situation, to support the patient’s efforts to express wishes regarding medical treatment, to value and encourage parental support and involvement, and to foster cooperation and mutual understanding. This may be difficult in situations in which parents and adolescents disagree about life-sustaining treatments such as organ transplantation or chemotherapy, but many such conflicts may be resolved by exploring the reasons for the disagreement. Overriding an adolescent’s wishes should be done very infrequently, and only after careful consideration of the potential consequences of unwanted interventions.

Decisions in Terminally Ill Adolescents

Most adolescents share end-of-life decision making with family members, although communication may be challenging because of a growing sense of independence. Open communication and flexibility about treatment preferences may help teens cope with fears and uncertainties. Development of an age-appropriate AD may support the patient’s emerging autonomy by clarifying the adolescent’s wishes, while fostering a collaborative process among the patient, family, and medical caregivers. From the time of diagnosis of a life-threatening condition through the end-of-life phase, children should be included in a developmentally tailored process of communication and shared decision-making that builds a foundation of mutual respect and trust.

RESEARCH

The central ethical challenge of pediatric research is the need to balance protection of children from research risk against the ethical imperative of conducting studies to better the lives of future children. Research is defined in the federal regulations as “a systematic investigation designed to develop or contribute to generalizable knowledge.” For any research to be performed, the risks should be minimized and reasonable with respect to any anticipated benefits to the subjects and the importance of the resulting knowledge. The fact that some children derive a direct benefit from participation in research must also be considered, making it important to distinguish research with the prospect of direct benefit from nontherapeutic pediatric research. Because children are a vulnerable population, there are restrictions on the research risks to which a child may be exposed that contrast with the risk level acceptable for research with consenting adults. These restrictions function by limiting the kind of research institutional review boards (IRBs) are permitted to approve and by specifying the conditions under which parent(s) have the moral and legal authority to permit a child to participate in research. Nontherapeutic research in children is the most ethically controversial because it holds no expected direct benefit for the subject. The prohibition against using a person (especially a child) solely as a means to an end has led some to argue that children should never be used in nontherapeutic research. The more widely held opinion is that children may be exposed to a limited degree of risk with IRB approval, parental permission, and assent if the child is capable. The federal regulations allow healthy children to participate in minimal-risk research regardless of the potential benefit to the child-subject. More
controversially, the regulations also state that children with a disorder or condition may be exposed to slightly more than minimal risk in nontherapeutic research if the child's experience is similar to everyday life with that condition and the anticipated knowledge is of vital importance for understanding that condition.

In pediatric research with the prospect of direct benefit, the risks must be justified by the anticipated benefit to the child, and the balance of anticipated benefit to the risk should be at least as favorable as that presented by available alternatives. The welfare of an individual child must always come before the scientific goals of the research study.

The regulations in the United States for the protection of human research subjects rest on 2 foundations: (1) independent review of the ethics and science of the research by an IRB prior to (2) voluntary and informed consent of the subject/participant. Although it is not amenable to regulation, the integrity of the investigator is probably the most important element contributing to the protection of human research subjects. The standard for informed consent in a research setting is higher than for clinical care because the risks and benefits are typically less clear, the investigator has a conflict of interest, and humans have historically been subjected to unauthorized risks when strict requirements for consent were not respected.

Adolescents who are competent may sometimes consent to be research subjects. Younger children may participate in a process of assent, but this does not imply that a child's signature on an assent document is necessarily a legal or ethical requirement. Children should be given the opportunity to dissent, particularly for nontherapeutic research, when there cannot be a claim that participation is in the child's interest. In the United States, national regulations require that reasonable efforts be made at least to inform children who are capable of understanding that participation is not part of their care and that, therefore, they are free to refuse to participate. In the rare case that the research offers a direct benefit to the child that would not otherwise be available, the regulations do not require child assent but only parental permission.

In addition to the protection that informed consent/parental permission is intended to provide, virtually all research involving human subjects in the United States is reviewed by an IRB, required by federal regulations for institutions receiving federal research funds and for drug research regulated by the U.S. Food and Drug Administration. For research that carries more than a minor increase over minimal risk without prospect of benefit to the child such that a local IRB cannot provide approval, there is a process for federal review of research that “presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.” Ultimately, the U.S. Secretary of Health and Human Services has the authority to approve such research.

**BALANCING MATERNAL AND FETAL INTERESTS**

Some situations require balancing of maternal health and well-being with those of the fetus/unborn child to reach an ethically sound decision. For instance, innovative surgical treatment of a prenatally diagnosed anomaly may help the fetus/unborn child survive, but in the process place the mother at risk of injury or of loss of the pregnancy. Alternatively, a pregnant woman may object to delivery by caesarian section for various reasons in spite of advice that it may protect the fetus/unborn child during birth. A third important situation involves risk-taking behaviors during pregnancy that are known to injure the developing fetus/unborn child, such as drug or alcohol use. These issues raise conflicts over clinicians' responsibility to the living, competent decision-maker—the pregnant mother—as opposed to the interests of the fetus/unborn child.

In certain cases, courts in the United States have decided that a woman can be required to undergo caesarian section against her will when the risk to her health is minimal and the benefit to the otherwise normal, near-term fetus/unborn child is clear, for example, in a case of placenta previa. Other factors, such as prematurity, have led to the opposite legal conclusion in otherwise similar situations because the benefit of intervention was less clear. In general, a clinician should not oppose a pregnant woman's refusal of a recommended intervention unless (1) the risk to the pregnant woman is minimal, (2) the intervention is clearly effective, and (3) the harm to the fetus/unborn child without the intervention would be certain, substantial, and irrevocable. Attempts should be made to persuade the pregnant woman to comply with recommendations in the interest of the fetus/unborn child when these 3 conditions exist, using support strategies such as the influence of other trusted caregivers, clergy, and/or ethics consultation/committee involvement. If these approaches fail and there is time, a clinician may seek judicial intervention as a last resort in the attempt to prevent harm to the fetus/unborn child.

Obstetricians and pediatricians may consider reporting women under child abuse or neglect statutes if ingesting alcohol or illicit drugs during pregnancy is felt to place the fetus/unborn child at risk of injury. However, clinicians must consider the likelihood of benefit from reporting, the harm to the child as well as to the mother if criminal charges or custody changes are sought, and the possible effects that reporting may have on driving pregnant women away from prenatal or postnatal care. The U.S. Supreme Court has held that drug testing of pregnant women without consent was a violation of the Fourth Amendment, which provides protection from unreasonable searches.

**JUSTICE AND PEDIATRIC ETHICS**

The most serious ethical problem in healthcare in the United States may be inequality in access to healthcare. Children are particularly vulnerable to this disparity, and pediatricians have a moral obligation to advocate for children as a class. Because children do not vote and do not have financial resources at their disposal, they are subject to a greater risk of being uninsured or underinsured. This lack of adequate and affordable healthcare has serious consequences in terms of death, disability, and suffering. The Affordable Care Act may help to ameliorate these problems in the United States. The per capita proportion of healthcare funding spent on adults greatly exceeds that spent on children, and Medicare is available to all adults who turn 65 yr old whereas Medicaid is limited to those beneath a specific income level. Federal dollars intended to support healthcare for children are generally administered and supplemented with state funds, which can create additional barriers. Pediatricians should be familiar with policy issues around the economics of child healthcare so that they will be better able to advocate for their own patients (see Chapter 1).

**EMERGING ISSUES**

The ready availability of information on the Internet has encouraged parents to become more involved in advocating for specific approaches to the healthcare of their children, requiring physicians to remain aware of the quality of these sources of information in order to adequately counsel parents on treatment choices. Because the range of aggressive, innovative, or exceedingly expensive therapies has increased, without necessarily providing clear benefit to the patient, pediatricians must exercise care and judgment before agreeing to pursue these interventions. A growing number of parents are refusing to immunize their children because of fear of adverse reaction to vaccine. This raises the ethical problem of the “free rider,” in which a child may benefit from herd immunity because others have been immunized without contributing to this public good. Outbreaks of preventable infectious disease have been detected in communities where vaccine refusal is prevalent. Pediatricians should manage this issue with ethical sensitivity, educating parents about the safety profile of vaccines and encouraging appropriate immunization. More confrontational approaches are not generally effective or ethically warranted. A second emerging issue relates to children as stem cell or solid organ donors. Here the risk/benefit balance should be carefully weighed, but in general, a permissive policy with regard to stem cell donation and a more restrictive approach to solid-organ donation are ethically justified. Finally, controversial medical and surgical interventions, such as growth attenuation of children with severe cognitive impairment in hopes of prolonging ability to care for them in the home setting, and disorders of sexual development require careful ethical consideration. Attitudes about emerging technologies and treatments
may be influenced by media coverage, special interest groups, and efforts by understandably desperate families to help their children. The clinician attempting to practice ethically must carefully consider all relevant facts in each case, and try to focus families and caregivers on a reasonable best interest assessment for the child. The tension between finding optimal policy for groups of children and doing the right thing for an individual child raises formidable ethical challenges in this context. Ethics consultation may be helpful to frame the issues and design ethically supportable approaches to care.

*Bibliography is available at Expert Consult.*
Cultural Issues in Pediatric Care

Linda Kaljee and Bonita F. Stanton

Pediatricians live and work in a multicultural world. Among the world’s 7 billion people residing in >200 countries, >6,000 languages are spoken. As the global population becomes more mobile and integrated, ethnic and economic diversity increases in all countries. From 1970 to 2000, the foreign-born population in the United States increased 3-fold. In the 2000 U.S. census, 25-30% of Americans self-identified as belonging to an ethnic or racial minority group. In 2010, 13% of the population was foreign born and 1 or both parents of 24% of children under age 17 yr is foreign born; the 40 million immigrants represents a 28% increase over the number in 2000. Whereas in 1920, 97% of immigrant families in the United States were from Europe or Canada as of 2010 more than 90% of immigrant families are from Asia and Latin America. Nonwhite children are projected to outnumber white children in the United States by the year 2030. Increased migration and diversity in the migrant pool is not limited to the United States; immigrants account for more than 15% of the population in >50 nations.

THE IMPORTANCE OF CULTURE TO MEDICAL PRACTICE

The concept of culture includes the ways in which a group of people share and understand their history, beliefs, and values, and engage in behaviors reflective of these shared worldviews. Although culture is not synonymous with language, ethnicity, nationality, or socioeconomic status, groups with similar backgrounds with respect to these characteristics often share cultural norms and beliefs.

Within cultures, there are frameworks for classifying and organizing kin (family), assigning roles and responsibilities based on age, gender, and other social groupings, and defining concepts such as prosperity, success, knowledge, causes of disease, and health. Disease typology, prevention and intervention efforts, and health practitioners are culturally defined. Health-related cultural-beliefs and practices are integrated within pluralistic health systems that include both biomedicine and traditional medicine.

Tables 4-1 to 4-3 display some cultural values associated with 4 populations in the United States: Latinos, Muslims, Native Americans, and African-Americans, illustrating both areas of significant overlap and great variation that are relevant to health perceptions and health seeking. Latinos may subscribe to the importance of “personalismo,” placing great importance on politeness in the face of stress and adversity. Thus expectations may include a display of warmth from their physician, including physical touching such as handshaking, placing hands on the shoulder, and occasionally hugging. By contrast, in the Muslim culture, for a person to touch the body of a member of the opposite gender, including on the arm or a pat on the shoulder, is considered highly inappropriate.

Despite the existence of shared values within a defined population group, there may be substantial variations within subgroups, such as the Latino national subgroups (e.g., Cuban, Puerto Rican, Dominican, Mexican), resulting in great variation in specific health-seeking behaviors. Likewise, within an overarching culture (“American”), persons who are economically and/or politically disenfranchised may use resistance, inverting the values of the dominant socioeconomic group. Such a reaction may include distrust of recommendations regarding healthcare from members of the perceived dominant or controlling group or class. Immunizations have been viewed with distrust among the poor in countries around the globe, as they were believed to be a form of birth control or sterilization and were often offered through institutions associated with “Western” and postcolonial rule. Within cultures, socially constructed categories of gender, sexuality, and age affect perceptions of an individual’s vulnerability to a particular disease or condition, as well as the individual’s access to health system resources. Adolescents girls living in cultures with strong taboos against premarital sexual relationships (e.g., Chinese, Muslim, Vietnamese) may not have social access to disease and birth control protection (e.g., condoms) resulting in increased risks for HIV, other sexually transmitted infections, and unwanted pregnancies.

There may also be significant generational differences between foreign-born parents and their American-raised children, particularly as these children go through adolescence. Such disparate experiences and cultural identities can result in a generational gap that decreases parent–child communication and subsequently lessens the important positive effects of communication on reducing substance use and engagement in sexual risk behaviors among youth.

Other values may be shared across disparate cultural groups. Multiple ethnic groups, including Latinos and Muslims, as well as Sudanese and Bengalis, share a cultural belief of fatalism, with strong implications for health-seeking behavior.

The perceived role of the physician may also differ between cultures. Pediatricians are trained to offer advice on child rearing, and studies have shown that parents look to pediatricians for this advice. However, parents of differing cultural backgrounds may not desire or may be reluctant to accept such advice.

NEWLY RECOGNIZED CULTURAL GROUPS

Groups that may or may not traditionally have been recognized as distinct cultural groups, (adolescents, gay/lesbian youth, transgender youth, street youth, deaf youth, etc.) have shared values which frequently have implications for health and health seeking. Failure on the part of the pediatrician to recognize accepted language and frame of reference of these groups may result in the unintentional use of offensive terminology or assumptions, leading to loss of the physician’s credibility or noncompliance from the patient.

THE CULTURE OF THE MEDICAL PROFESSION

The profession of medicine also has a distinct culture. Like other cultural groups, physicians have a distinct “language” and share a common history, admiring the same role models, sharing the same preparatory courses that must be mastered for entrance into training for the profession, and subscribing to a common meaning of “competence” in medical practice. Physicians learn a new way to describe health and illness, requiring a new vocabulary and a prescribed pattern to the narrative history, which is not shared by those outside medicine. Physician reliance on “evidence-based practice” carries the implication that it is synonymous with truth or real knowledge. Of particular importance in the relationship with patients has been the lack of physician insight into the existence of a physician culture and the potential biases that may be inherent to that culture.

Although physicians around the world recognize the great strides that have been made in child survival through the use of oral rehydration therapy in the treatment of dehydrating diarrheal diseases, parents are often anxious because the treatment does not stop the diarrhea. Physicians may be dependent on a particular style of communication...
### Table 4-1 | Cultural Values* Relevant to Health and Health-Seeking Behavior

<table>
<thead>
<tr>
<th>CULTURAL GROUP</th>
<th>RELEVANT CULTURAL NORMS</th>
<th>Description of Norm</th>
<th>Consequences of Failure to Appreciate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latino</td>
<td>Fatalismo: Fate is predetermined, reducing belief in the importance of screening and prevention</td>
<td>Loss of opportunity to work with the church as an ally in healthcare</td>
<td>Nonadherence to therapy, failure to make follow-up visits</td>
</tr>
<tr>
<td></td>
<td>Sympatia: Politeness/kindness in the face of adversity—expectation that the physician should be polite and pleasant, not detached</td>
<td>Agreement with the physician may be difficult if patient is incapable</td>
<td>Refusal to divulge important parts of medical history, dissatisfaction with treatment</td>
</tr>
<tr>
<td></td>
<td>Personalismo: Expectation of developing a warm, personal relationship with the clinician, including introductory touching</td>
<td>Advice/instructions given only to the parent and not to others involved in health decision making may not be effective</td>
<td>Mistaking a deferential nod of the head/not asking questions for understanding; anger at not receiving due signs of respect</td>
</tr>
<tr>
<td></td>
<td>Respecto: Deferential behavior on the basis of age, social stature, and economic position, including reluctance to ask questions</td>
<td>Advice regarding discipline may be disregarded if it is inconsistent with perceived norms; other parenting styles may not be effective</td>
<td>Unnecessary conflict, inability to reach a decision</td>
</tr>
<tr>
<td></td>
<td>Familismo: Needs of the extended family outrank those of the individual, and thus family may need to be consulted in medical decision making</td>
<td>Refusal of medication, religious effrontery</td>
<td>Patient discomfort, seeking care elsewhere</td>
</tr>
<tr>
<td>Muslim</td>
<td>Fasting during the holy month of Ramadan: fasting from sunrise to sundown, beginning during the teen years. Women are exempted during pregnancy, lactation, and menstruation, and there are exemptions for illness, but an exemption may be associated with a sense of personal failure</td>
<td>Inappropriate therapy; will not take medicines during daytime misinterpreted as noncompliance; misdiagnosed</td>
<td>Deep personal outrage, seeking alternative care</td>
</tr>
<tr>
<td></td>
<td>Modesty: Women’s body including hair, body, arms, and legs not to be seen by men other than in immediate family. Female chaperone and/or husband must be present during exam and only that part of the body being examined should be uncovered</td>
<td>Inpatient noncompliance, physicians will be consulted as another family member cannot intervene</td>
<td>Patient discomfort, seeking care elsewhere</td>
</tr>
<tr>
<td></td>
<td>Touch: Forbidden to touch members of the opposite sex other than close family. Even a handshake may be inappropriate</td>
<td>Advice regarding discipline may be disregarded if it is inconsistent with perceived norms; other parenting styles may not be effective</td>
<td>Unnecessary intensification of grief and loss</td>
</tr>
<tr>
<td></td>
<td>After death, body belongs to God: Postmortem exam will not be permitted unless required by law; family may wish to perform after-death care</td>
<td>Refusal to divulge important parts of medical history, religious effrontery</td>
<td>Allopathic medicine will be rejected if it conflicts with religious beliefs, family may not seek healthcare</td>
</tr>
<tr>
<td></td>
<td>Cleanliness essential before prayer: Individual must perform ritual ablutions before prayer, especially elimination of urine and stool. Nurse may need to assist in cleaning if patient is incapable</td>
<td>Refusal to divulge important parts of medical history, religious effrontery</td>
<td>Child’s mother or even both parents may not be able to make decisions about child’s care; emergency decisions may require additional time</td>
</tr>
<tr>
<td></td>
<td>God’s will: God causes all to happen for a reason, and only God can bring about healing</td>
<td>Refusal to divulge important parts of medical history, religious effrontery</td>
<td>Refusal of medication, religious effrontery</td>
</tr>
<tr>
<td></td>
<td>Patriarchal, extended family: Older male typically is head of household, and family may defer to him for decision making</td>
<td>Refusal to divulge important parts of medical history, religious effrontery</td>
<td>Refusal of medication, religious effrontery</td>
</tr>
<tr>
<td></td>
<td>Halal (permitted) vs. harem (forbidden) foods and medications: Foods and medicine containing alcohol (some cough and cold syrups) or pork (some gelatin-coated pills) are not permitted</td>
<td>Refusal to divulge important parts of medical history, religious effrontery</td>
<td>Refusal of medication, religious effrontery</td>
</tr>
<tr>
<td>Native</td>
<td>Nature provides the spiritual, emotional, physical, social, and biologic means for human life; by caring for the earth, Native Americans will be provided for. Harmonious living is important</td>
<td>Spiritual living is required of Native Americans; if treatments do not reflect this view, they are likely not to be followed</td>
<td>Patient discomfort, seeking care elsewhere</td>
</tr>
<tr>
<td>American</td>
<td>Passive forbearance or right of the individual to choose his or her path: Another family member cannot intervene</td>
<td>Spiritual living is required of Native Americans; if treatments do not reflect this view, they are likely not to be followed</td>
<td>Patient discomfort, seeking care elsewhere</td>
</tr>
<tr>
<td></td>
<td>Natural unfolding of the individual: Parents further the development of their children by limiting direct interventions and viewing their natural unfolding</td>
<td>Many pediatric preventive practices will run counter to this philosophy</td>
<td>Unnecessary conflict, inability to reach a decision</td>
</tr>
<tr>
<td></td>
<td>Talking circle format to decision-making: Interactive learning format including diverse tribal members</td>
<td>Many pediatric preventive practices will run counter to this philosophy</td>
<td>Unnecessary conflict, inability to reach a decision</td>
</tr>
<tr>
<td>African-</td>
<td>Great heterogeneity in beliefs and culture among African-Americans</td>
<td>Risk of stereotyping and/or making assumptions that do not apply to a specific patient or family</td>
<td>Risk of stereotyping and/or making assumptions that do not apply to a specific patient or family</td>
</tr>
<tr>
<td>American</td>
<td>Extended family and variations in family size and child care arrangements are common; matriarchal decision making regarding healthcare</td>
<td>Advice/instructions given only to the parent and not to others involved in health decision making may not be effective</td>
<td>Advice/instructions given only to the parent and not to others involved in health decision making may not be effective</td>
</tr>
<tr>
<td></td>
<td>Parenting style often involves stricter adherence to rules than seen in some other cultures</td>
<td>Advice regarding discipline may be disregarded if it is inconsistent with perceived norms; other parenting styles may not be effective</td>
<td>Advice regarding discipline may be disregarded if it is inconsistent with perceived norms; other parenting styles may not be effective</td>
</tr>
<tr>
<td></td>
<td>History-based widespread mistrust of medical profession and strong orientation toward culturally specific alternative/complementary medicine</td>
<td>Inpatient noncompliance, physicians will be consulted as a last resort</td>
<td>Inpatient noncompliance, physicians will be consulted as a last resort</td>
</tr>
<tr>
<td></td>
<td>Greater orientation toward others; the role of an individual is emphasized as it relates to others within a social network</td>
<td>Compliance may be difficult if the needs of 1 individual are stressed above the needs of the group</td>
<td>Compliance may be difficult if the needs of 1 individual are stressed above the needs of the group</td>
</tr>
<tr>
<td></td>
<td>Spirituality/religiosity important; church attendance central in most African-American families</td>
<td>Loss of opportunity to work with the church as an ally in healthcare</td>
<td>Loss of opportunity to work with the church as an ally in healthcare</td>
</tr>
</tbody>
</table>
and they may miss information from patients using alternative narrative styles. Likewise, the physician–researcher forms questions through the prism of the physician–researcher’s own beliefs and literature, thereby reducing the likelihood of exploring alternative explanations or questions. Even though vast segments of the world’s population understand disease as an imbalance of “hot” and “cold,” this belief system has not been well-represented in contemporary medical research.

**CULTURAL COMPETENCE**

Physicians and patients bring to their interaction personal and professional values from multiple cultural systems that have significant implications for the delivery of healthcare. Consequently, physician “cultural competence” is critical to a successful patient–provider interaction (Fig. 4-1). Campinha-Bacote’s model for understanding and assessing culturally competency is frequently used in education and research: (1) learning to value and understand other cultures, in part through self-awareness of one’s own cultural values (“cultural awareness”); (2) learning basic fundamentals about other cultures, particularly those of the patients with whom the physician will interact (“cultural knowledge”); (3) developing the ability to apply cultural knowledge in patient encounters (“cultural skills”); (4) seeking exposure to cross-cultural interactions (“cultural encounters”); and (5) being motivated to achieve all of the previous (“cultural desire”). This framework provides an important guide to pediatric education and practice and, thus, will serve as the outline for the remainder of this chapter.

**Cultural Awareness**

Recognition of the importance of differing cultural expectations and explanations is critical to a pediatrician’s successful interactions with patients. Among many cultures (e.g., Muslim), kinship is of great importance and decision making may involve the extended family. The erroneous belief on the part of a physician that a mother may execute independent decision making in relation to her child’s healthcare (when in fact she may not be entitled to such a role in her family or culture) may result in an apparent noncompliance on the part of the patient, etc.

**Cultural Knowledge**

Physicians and patients have differing definitions of health and illness and differing concepts of the origins of disease and therapeutic responses. Understanding the patient perspective will both increase

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**Table 4-1** Cultural Values* Relevant to Health and Health-Seeking Behavior—cont’d

<table>
<thead>
<tr>
<th>CULTURAL GROUP</th>
<th>Description of Norm</th>
<th>RELEVANT CULTURAL NORMS</th>
<th>Consequences of Failure to Appreciate</th>
</tr>
</thead>
<tbody>
<tr>
<td>East and Southeast Asian</td>
<td>Long history of eastern medicines (e.g., Chinese medicine) as well as more localized medical traditions</td>
<td>Parents may engage with multiple health systems (Western biomedical and traditional) for treatment of symptoms and diseases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Extended families and care networks. Grandparents may provide day-to-day care for children while parents work outside of the home</td>
<td>Adolescents may be reluctant to talk about issues of sexuality, pregnancy, birth control with physicians</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sexually conservative. Strong taboos for premarital sexual relationships, especially for women</td>
<td>Recent immigrants or native populations may have less knowledge regarding pregnancy prevention, sexually transmitted infections, and HIV.</td>
<td></td>
</tr>
<tr>
<td>Infant/child feeding practices may overemphasize infant’s or child’s need to eat a certain amount of food to stay “healthy”</td>
<td>Guidelines for child nutrition and feeding practices may not be followed out of concern for child’s well-being</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saving face. This is a complex value whereby an individual may lose prestige or respect of a third party when a second individual says negative or contradictory statements</td>
<td>Avoid statements that are potentially value laden or imply a criticism of an individual. Use statements such as “We have now found that it is better to …” rather than criticizing a practice</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adherence to these or other beliefs will vary among members of a cultural group based on nation of origin, specific religious sect, degree of acculturation, age of patient, etc.

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**Table 4-2** Examples of Disease Beliefs or Practices

<table>
<thead>
<tr>
<th>CULTURAL GROUP</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latino</td>
<td>Use of traditional medicines (nopales or cooked prickly pear cactus as a hypoglycemic agent) along with allopathic medicine</td>
</tr>
<tr>
<td></td>
<td>Recognition of disorders not recognized in Western allopathic medicine (empacho, in which food adheres to the intestines or stomach), which are treated with folk remedies but also brought to the pediatrician</td>
</tr>
<tr>
<td></td>
<td>Cultural interpretation of disease (caida de mollera or fallen fontanel) as a cultural interpretation of severe dehydration in infants</td>
</tr>
<tr>
<td>Muslim</td>
<td>Female genital mutilation: practiced in some Muslim countries; the majority do not practice it and it is not a direct teaching of the Koran</td>
</tr>
<tr>
<td></td>
<td>Koranic faith healers: use verses from the Koran, holy water, and specific foods to bring about recovery</td>
</tr>
<tr>
<td>Native American</td>
<td>Traditional “interpreters” or “healers” interpret signs and answers to prayers. Their advice may be sought in addition or instead of allopathic medicine</td>
</tr>
<tr>
<td></td>
<td>Dreams are believed to provide guidance; messages in the dream will be followed</td>
</tr>
<tr>
<td>East and Southeast Asian</td>
<td>Concepts of “hot” and “cold,” whereby a combination of hot and cold foods and other substances (e.g., coffee, alcohol) combine to cause illness. One important aspect is that Western medicines are considered hot by Vietnamese and, therefore, nonadherence may occur if it is perceived that too much of a medicine will make their child’s body hot. Note: Hot and cold do not refer to temperatures, but are a typology of different foods; for example, fish is hot and ginger is cold.</td>
</tr>
<tr>
<td></td>
<td>Foods, teas, and herbs are also important forms of medicine because they provide balance between hot and cold medical research.</td>
</tr>
</tbody>
</table>
Table 4-3

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>REMEDY</th>
<th>KNOWLEDGE, % (N = 107)</th>
<th>USE, % (N = 107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Acetaminophen*</td>
<td>98</td>
<td>77.6</td>
</tr>
<tr>
<td></td>
<td>Cool bath*</td>
<td>85</td>
<td>48.3</td>
</tr>
<tr>
<td></td>
<td>Isopropyl alcohol*</td>
<td>71</td>
<td>38.3</td>
</tr>
<tr>
<td></td>
<td>Cool drinks/popsicles†</td>
<td>11.2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Undress child†</td>
<td>10.3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen†</td>
<td>10.3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Warm feet†</td>
<td>8.4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Potatoes or onions in socks†</td>
<td>6.5</td>
<td>0</td>
</tr>
<tr>
<td>Colic</td>
<td>Catnip*</td>
<td>34.6</td>
<td>8.4</td>
</tr>
<tr>
<td></td>
<td>Senna extract*</td>
<td>25.2</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>Other (asafetida, paregoric, or bicarbonate)†</td>
<td>13.1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Chamomile*</td>
<td>7.5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Walk†</td>
<td>6.5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Cigarette smoke†</td>
<td>5.6</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Simethicone drops†</td>
<td>4.7</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Vacuum/steam†</td>
<td>3.7</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Cover head†</td>
<td>3.7</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Massage†</td>
<td>2.8</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Gripe water†</td>
<td>1.9</td>
<td>0</td>
</tr>
<tr>
<td>Teething</td>
<td>Nonprescription benzocaine gel*</td>
<td>97.2</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Teething object†</td>
<td>35.2</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td>Whiskey†</td>
<td>34.6</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>Penny†</td>
<td>16.8</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Ice cubes/popsicles†</td>
<td>13.3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Egg†</td>
<td>11.4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Spices (asafetida, cloves, or vanilla)†</td>
<td>4.8</td>
<td>0</td>
</tr>
</tbody>
</table>

*Responses given in closed-ended questions.
†Responses given in open-ended questions.


the likelihood of correct diagnosis and patient adherence to therapy and decrease the possibility of misdiagnosis. The belief that becoming chilled causes dysentery is common among rural Chinese, and medical advice that directly challenges or runs contrary to this belief may be disregarded. Likewise, diarrhea among Bangladeshi children during teething may be regarded as normal and would not be identified as a health issue. Thus, asking the parent if the child has been ill might not reveal the presence of diarrhea. Rubbing a coin against a child’s skin is thought by some parents in Asia to reduce fever. Failure by the pediatrician to recognize the practice of coining could lead to the erroneous...
diagnosis of a rash or child abuse. In some instances, particularly in relation to developmental and emotional disorders, the manifestation of symptoms and/or recognition of symptoms by parents or other caregivers may be culturally defined. Autism is a condition characterized by communication and socializing disabilities. Yet expectations of children's language and social skills development are culturally defined, resulting in potentially later identification by family members of a child's disabilities and subsequently delayed treatment seeking.

**Cultural Skill**

Describing a diagnostic or therapeutic course of action that respects cultural beliefs but is consistent with good medical practice can be challenging. Common among many Latino groups is the belief of *empacho*, a condition wherein food is "stuck" to the stomach or intestinal wall, resulting in obstruction. The condition is believed to cause nausea, vomiting, diarrhea, and anorexia. Although many Latino parents would take a child with *empacho* to the physician for treatment, in Western settings, a pediatrician diagnosing the condition as viral gastroenteritis might only advise supportive management, leaving the parents perplexed and with no option but to seek independent treatment from an alternative or traditional healer. A culturally skilled pediatrician might suggest partnering with the traditional healer in such a situation. Likewise, in response to parents subscribing to a belief in fatalism and, consequently, a notion that preventive medicine or screening is not necessary, a skilled pediatrician might suggest that screening is the mechanism through which their destiny is intended to be reached. Referrals for services may also be affected by a patient's culture and history. The need for psychologic services may be rejected because of cultural stigmas regarding psychological disorders. Likewise, referrals for HIV or sexually transmitted infection testing may be more likely rejected by gay adolescent men from cultures in which homosexuality is highly stigmatized.

Central to "cultural skill" is the employment of language fully comprehended by the child's parents. This goal is best realized if the pediatrician is at least conversant in the parent's language, and thus a requirement for a second language is a reasonable goal for physicians. Familiarity with a language should not be confused with fluency or even competency. Professional interpreters should be available and accessed to overcome the language barriers. Ad hoc use of individuals at the workplace who are known to possess skill in the indicated language and/or use of telephone interpreter services may suffice if a professional interpreter is not available. A genuinely bilingual family member or friend may be helpful, but issues of confidentiality, disruption of social roles, and uncertain or inaccurate translation of medical terms may pose serious problems. Medical errors occur at a significantly higher rate among non–English speaking patients when nonprofessional translators (e.g., family members) are used to obtain a history or give medical advice.

**Cultural Encounters**

Although cultural knowledge may be acquired through didactic training, the development of cultural skills requires experience that can only be gained through repeated "cultural encounters." Nonminority clinicians provide lower quality of care to Latino and African-American patients, with these children being less likely to receive analgesia and/or nebulizers for asthma. Latino mothers have reported clinician attitudes as a major barrier to seeking care for their children. Participation by physicians in diverse medical educational settings and experience in community clinics has been shown to predict increased cultural knowledge. Cultural knowledge and participation in diverse educational settings, and Latino ethnicity and bilingual skills likewise predict cultural awareness. Cultural awareness predicts culturally competent actions. Consistent with observations that cultural competence may not be valued in the traditional medical culture is the observation that higher specialty training (e.g., subspecialty training among internists compared to general physicians, family medicine, or internal medicine generalists) predicted less cultural awareness. Children who receive care from practice sites with the highest cultural competence scores are less likely to underutilize preventive asthma medications.

**Cultural Desire**

Cultural competence is not something that can be achieved and retained in the absence of continued effort. The recognition that culture is integral to health and healing, and to disease and sickness, is central to the concept of "cultural competence." Understanding of the role of culture in health outcomes is nascent; it is not yet known why less acculturated Latinos in the United States demonstrate significantly lower rates of low birthweight, depression, tobacco use, illicit drug use, and older age for sexual debut compared to those who are more acculturated. Likewise, less acculturation among Asian children is associated with lower prevalence of chronic illness. Such findings expose the complexities between individuality, environment, cultures, and biology, and how these integrated factors can affect health-related behaviors and health outcomes.

*Bibliography is available at Expert Consult.*
Bibliography


Routine, scheduled care of well infants, children, and adolescents is an essential prevention effort for children and youth worldwide. Children’s constantly changing development lends added value to regular and periodic encounters between children and their families and practitioners of pediatric healthcare. Health supervision visits from birth to age 21 yr are the platform for a young person's healthcare. The provision of well care in the medical home, fosters strong relationships between the clinic or practice and the child and family, enabling the provision of appropriate surveillance, screening, and sick care.

To assure the optimal health of the developing child, pediatric care in the United States and other countries evolved into regularly scheduled visits to assure adequate nutrition, detect and immunize against infectious diseases, and observe the child’s development. Assessment of immunizations, nutrition and developmental status remain essential elements of the well-child health supervision visit, but changes in the population’s health have led to the addition of other components to the content of today’s well-child encounter. Preventive care for children and youth is a component of contemporary U.S. health reform activities; this approach offers great opportunity for health cost savings.

A healthy economy requires educated and healthy workers. For children to have a successful educational experience, they must have both physical and emotional health. Educational success is also tied to early childhood developmental competence. Thus health supervision well-child care plays a vital role in promoting adult health, a concept endorsed by business leaders.

Adversity impairs development and adverse factors in life experience increase the risk of disease. Adults who experienced abuse, violence, or other stressors as children have an increased risk for depression, heart disease, and other morbidities. Biology informs us that stress leads to increased heart rate and blood pressure, and increased levels of inflammatory cytokines, cortisol, and other stress hormones, all of which impair brain activity, immune status, and cardiovascular function. There are both a causal model and evidence that
adverse childhood events, including those that could have been prevented, adversely impact the life course.

PERIODICITY

The frequency and content for well-child care activities are derived from evidence-based practice and research. In addition, federal agencies and professional organizations, such as the American Academy of Pediatrics (AAP), have developed evidence informed, expert consensus guidelines for care. The Recommendations for Preventive Pediatric Health Care or Periodicity Schedule (Fig. 5-1) is a compilation of recommendations listed by age-based visits. It is intended to guide practitioners of pediatric primary care to perform certain services and make observations at age-specific visits and it designates the standard for preventive services for children and youth according to the U.S. health reform legislation, the Affordable Care Act of 2010.

GUIDELINES

Comprehensive guides for care of well infants, children, and adolescents have been developed, based on the Periodicity Schedule, which expand and further recommend how practitioners might accomplish the tasks outlined in the Periodicity Schedule. In the United States, the current guideline standard is *The Bright Futures Guidelines for Health Supervision of Infants, Children, and Adolescents*, 4th edition. These guidelines were developed by the AAP under the leadership of the Maternal Child Health Bureau of the U.S. Department of Health and Human Services, in collaboration with the National Association of Pediatric Nurse Practitioners, the American Academy of Family Physicians, the American Medical Association, the American Academy of Pediatric Dentistry, Family Voices, and others.

TASKS OF WELL-CHILD CARE

The well-child encounter intends to promote the physical and emotional well-being of children and youth. Child health professionals, including pediatricians, family medicine physicians, nurse practitioners, and physician assistants, take advantage of the opportunity well-child visits provide to elicit parental questions and concerns, gather relevant family and individual health information, perform a physical examination, and initiate screening tests.

The tasks of each well-child visit include:

- Disease detection
- Disease prevention
- Health promotion
- Anticipatory guidance

To achieve these outcomes, healthcare professionals employ techniques to screen for disease, screen for risk of disease, and provide advice about healthy behaviors. These activities lead to the formulation of appropriate anticipatory guidance and health advice.

Clinical detection of disease in the well-child encounter is accomplished by both surveillance and screening. In well-child care, surveillance occurs in every health encounter and is enhanced by repeated visits and observations with advancing developmental stages. It relies on the experience of a skilled clinician over time. Screening is a more formal process utilizing some form of tool that has been validated and has known sensitivity and specificity. For example, anemia surveillance is accomplished through taking a dietary history and seeking signs of anemia in the physical examination. Anemia screening is done by hematocrit or hemoglobin tests. Developmental surveillance relies on the observations of parents and the watchful eyes of providers of pediatric healthcare who are experienced in child development. Developmental screening uses a structured developmental screening tool by personnel trained in its use or in the scoring and interpretation of parent report questionnaires.

The second essential action of the well-child encounter, disease prevention, may include both primary prevention activities applied to a whole population and secondary prevention activities aimed at patients with specific factors of risk. For example, counseling about reducing fat intake is appropriate for all children and families. Counseling is intensified for overweight and obese youth or in the presence of a family history of hyperlipidemia and its sequelae. The child and adolescent healthcare professional needs to individualize disease prevention strategies to the specific patient, family, and community.

Health promotion and anticipatory guidance activities distinguish the well-child health supervision visit from all other encounters with the healthcare system. Disease detection and disease prevention activities are germane to all interactions of children with physicians and other healthcare providers, but health promotion and anticipatory guidance shift the focus to wellness and to the strengths of the family (e.g., what is being done well and how this might be improved). This approach is an opportunity to help the family address relationship issues, broach important safety topics, access community services, and engage with extended family, school, neighborhood, and church.

It is not possible to cover all the topics suggested by comprehensive guidelines such as *Bright Futures* in the average 18 min well-child visit. Child health professionals must prioritize the most important topics to cover. Consideration should be given to a discussion of:

- The agenda the parent or child brings to the health supervision visit.
- The topics where evidence suggests counseling is effective in behavioral change.
- The topics where there is a clear rationale for the issue’s critical importance to health, for example, sleep environment to prevent sudden infant death syndrome or attention to diet and physical activity.
- A summary of the child’s progress in emotional and social development, physical growth, and strengths.
- Issues that address the questions, concerns, or specific health problems relevant to the individual family.
- Community-specific problems that could significantly impact the child’s health (e.g., neighborhood violence from which children need protection or absence of bike paths that would promote activity).

It is important to note that this approach is directed at all children, including those with special health needs. Children with special health needs are no different from other children in their need for guidance about healthy nutrition, physical activity, progress in school, connection with friends, a healthy sense of self-efficacy, and avoidance of risk-taking behaviors. The coordination of specialty consultation, medication monitoring, and functional assessment, which should occur in their periodic visits, needs to be balanced with a discussion of the child’s unique ways of accomplishing the emotional, social, and developmental tasks of childhood and adolescence. Comprehensive integrated care planning for children and youth with special healthcare needs supports partnerships between medical homes and families and youth through goal setting and negotiating next steps. In this process, chronic condition management and health surveillance (including adolescent engagement and planning for transition to adult care) occur within an effective patient care relationship, partnering to improve health outcomes and efficiencies of care provision.

INFANCY AND EARLY CHILDHOOD

Nutrition, physical activity, sleep, safety, and emotional, social, and physical growth, along with parental well-being, are critical for all children. For each well-child visit, there are topics that are specific to individual children based on their age, family situation, chronic health condition, or a parental concern, for example, sleep environment to prevent sudden infant death syndrome, activities to lose weight, and fences around swimming pools. Attention should also be focused on the family milieu, including screening for parental depression (especially maternal postpartum depression) and other mental illness, family violence, substance abuse, nutritional inadequacy, or lack of housing. These issues are essential to the care of young children.

Answering parents’ questions is the most important priority of the well-child visit. Promoting family-centered care and partnership with parents increases the ability to elicit parent concerns, especially about their child’s development, learning, and behavior. It is important to identify children with developmental disorders as early as possible.

Developmental surveillance at every visit combined with a structured developmental screening, neuromuscular screening and autism screening at some visits is a way to improve diagnosis, especially for some of
Chapter 5: Maximizing Children’s Health: Screening, Anticipatory Guidance, and Counseling

Figure 5-1 Recommendations for Preventive Pediatric Health Care (From Bright Futures/American Academy of Pediatrics. Copyright 2014, American Academy of Pediatrics, Elk Grove Village, IL.)

These guidelines are consistent with the American Academy of Pediatrics (AAP) and Bright Futures. The AAP continues to endorse the importance of preventive care in comprehensive health supervision and the need to avoid opportunities to save time by using abbreviated guidelines.

The recommendations in this statement do not indicate an exclusion or change of treatment or standards of medical care. Variation, taking into account individual circumstances, may be appropriate.

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2014 Recommendations for Preventive Pediatric Health Care

Bight Futures/American Academy of Pediatrics

Figure 5-1 Recommendations for preventive pediatric healthcare. (From Bright Futures/American Academy of Pediatrics. Copyright 2014, American Academy of Pediatrics, Elk Grove Village, IL.)
the more subtle delays or autism spectrum disorders where early intervention is believed to be associated with reduced morbidity.

MIDDLE CHILDHOOD AND ADOLESCENCE
As the child enters school-age years, additional considerations emerge. Attention to developing autonomy requires fostering a clinician–patient relationship separate from the clinician–child-family relationship with increasing needs for privacy and confidentiality as the child ages.

The health behaviors that most significantly impact adolescent and adult morbidity and mortality are inadequate physical activity, poor nutrition, sexual-related behaviors, substance use and abuse (including tobacco), unintentional injury-related behaviors, and intentional injury-related behaviors. Emotional well-being and early diagnosis and treatment of mental health problems are equally important, with attention to the developmental tasks of adolescence (competence at school and other activities, connection to friends and family, autonomy, empathy, and a sense of self-worth).

OFFICE INTERVENTION FOR BEHAVIORAL AND MENTAL HEALTH ISSUES
One-fifth of primary care encounters with children are for a behavioral or mental health problem, or are sickness visits complicated by a mental health issue. Pediatricians require increased knowledge for diagnosis, treatment, and referral criteria for attention-deficit/hyperactivity disorder (see Chapter 33), depression and other mood disorders (see Chapter 26), anxiety (see Chapter 25), and conduct disorder (see Chapter 29), as well as an understanding of the pharmacology of the most frequently prescribed psychotropic medications. Familiarity with available local mental health services and clinicians and knowledge of the types of services indicated are important for effective consultation or referral. Encouragement of behavioral change is also an important responsibility of the clinician. Motivational interviewing provides a structured approach that has been designed to help patients and parents identify the discrepancy between their desire for health and their behavioral choices. It also allows the clinician to use proven strategies that lead to a patient-initiated plan for change.

STRENGTH-BASED APPROACHES AND FRAMEWORK
Questions about school or extracurricular accomplishments or competent personal characteristics should be integrated into the content of the well child visit. Such inquiries set a positive context for the visit, deepen the partnership with the family, acknowledge the child's healthy development, and facilitate discussing social–emotional development with children and their parents. There is a strong relationship between appropriate social–emotional development (e.g., children's strong connection to their family, social friends, and mentors; competence; empathy; and appropriate autonomy) and decreased participation in all the risk behaviors of adolescence (related to drugs, sex, and violence). An organized approach to the identification and encouragement of a child's strengths during health supervision visits provides both the child and parent with an understanding of how to promote healthy achievement of the developmental tasks of childhood and adolescence. Children with special health needs often have a different timetable, but they have an equal need to be encouraged to develop strong family and peer connections, competence in a variety of arenas, ways to do things for others, and appropriate independent decision making.

OFFICE SYSTEM CHANGE FOR QUALITY IMPROVEMENT
Some of the office strategies to improve the preventive services delivered to children and youth include screening schedules and parent handouts, flow sheets, registries, and the use of parent and youth previsit questionnaires. Such tools are available in The Bright Futures Guidelines Toolkit and online previsit tools are under construction. These efforts are part of a larger national effort that is built on a coordinated team approach in the office setting and the use of continuous measurement for improvement.

EVIDENCE
Available evidence should be utilized in developing health-promotion and disease-detection recommendations. Revisions to the AAP’s Periodicity Schedule undergo rigorous evidence assessment; however, many highly valued well-child care activities have not been evaluated for efficacy. Lack of evidence is most often related to absence of study and does not define lack of benefit. Thus the clinical encounter with the well child is also guideline- and recommendation-driven and requires the integration of clinician goals, family needs, and community realities in seeking better health for the child. The rationale for well-child care activities is a balance of evidence from research, clinical practice guidelines, professional recommendations, expert opinion, experience and knowledge of the needs of the patient population in the context of community assets and challenges. Clinical or counseling decisions and recommendations may also be based on legislation (seat belts), on common sense measures not likely to be studied experimentally (lowering water heater temperatures), or on the basis of relational evidence (television watching associated with violent behavior in young children). Most important, sound clinical and counseling decisions are responsive to family needs and desires, and support “patient-centered decision making.”

CARING FOR THE CHILD AND YOUTH IN THE CONTEXT OF THE FAMILY AND COMMUNITY
A successful primary care practice for children incorporates families, is family centered, and embraces the concept of the medical home. A medical home is defined by the AAP as primary care that is accessible, continuous, comprehensive, family centered, coordinated, compassionate, and culturally effective. In a medical home, a pediatrician works in partnership with the family and patient to assure that all medical and nonmedical needs of the child are met. Through this partnership, the child healthcare professional helps the family/patient access and coordinate specialty care, educational services, out-of-home care, family support, and other public and private community services that are important to the overall health of the child and family.

Ideally, health promotion activities occur not only in the medical home, but also in partnership with community members and other health and education professionals. This rests on a clear understanding of the important role that the community plays in supporting healthy behaviors among families. Communities where children and families feel safe and valued, and have access to positive activities and relationships, provide the important base that the healthcare professional can build on and refer to for needed services that support health but are outside the realm of the healthcare system or primary care medical home. It is important for the medical home and community agencies to identify mutual resources, communicate well with families and each other, and partner in designing service delivery systems. This interaction is the practice of community pediatrics, whose unique feature is its concern for all of the population: those who remain well but need preventive services, those who have symptoms but do not receive effective care, and those who do seek medical care either in a physician's office or in a hospital.

Bibliography is available at Expert Consult.

5.1 Injury Control

Frederick P. Rivara and David C. Grossman

In all high-income countries of the world, and in many low- and middle-income countries, injuries are the most common cause of death during childhood and adolescence beyond the first few months of life and represent 1 of the most important causes of preventable pediatric morbidity and mortality in the United States (see Table 1-2 in Chapter 1 and Fig. 5-2). The identification of risk factors for injuries has led to the development of successful programs for prevention and control. Strategies for injury prevention and control should be pursued
Bibliography


by the pediatrician in the office, emergency department, hospital, and community setting and be done in a multidisciplinary, multifaceted fashion.

**INJURY CONTROL (FORMERLY CALLED ACCIDENT PREVENTION)**

Injuries have defined risk and protective factors that can be used to define prevention strategies. The term accidents implies an event occurring by chance, without pattern or predictability. In fact, most injuries occur under fairly predictable circumstances to high-risk children and families. Most injuries are preventable.

The reduction of morbidity and mortality from injuries can be accomplished not only through primary prevention (averting the event or injury in the first place), but also through secondary and tertiary prevention. The latter 2 approaches include appropriate emergency medical services for injured children; regionalized trauma care for the child with multiple injuries, severe burns, or traumatic brain injury; and specialized pediatric rehabilitation services that attempt to return children to their previous level of functioning.

Injury control also encompasses intentional injuries (assaults and self-inflicted injuries). These injuries are important in adolescents and young adults, and in some populations, they rank first or second as causes of death in these age groups. Many of the same principles of injury control can be applied to these problems; for example, limiting access to firearms may reduce both unintentional shootings and suicides.

**SCOPE OF THE PROBLEM**

**Mortality**

In the United States, injuries cause 41% of deaths among 1-4 yr old children and 3.5 times more deaths than the next leading cause, congenital anomalies. For the rest of childhood and adolescence up to the age of 19yr, 63% of deaths are a result of injuries, more than all other causes combined. In 2010, injuries caused 13,819 deaths (16 deaths per 100,000) among individuals 19yr old and younger in the United States (Table 5-1), resulting in more years of potential life lost than any other cause. Unintentional injuries remained the leading cause of death among those <24yr in 2014 (see Table 1-2).

Motor vehicle injuries lead the list of injury deaths among school-age children and adolescents, and are the second leading cause of injury death for those ages 1-4yr. In children and adults, motor vehicle occupant injuries account for the majority of these deaths. During adolescence, occupant injuries are the leading cause of injury death, accounting for >50% of unintentional trauma mortality in this age group.

Drowning ranks second overall as a cause of unintentional trauma deaths among those ages 1-14yr, with peaks in the preschool and later teenage years (see Chapter 74). In some areas of the United States, drowning is the leading cause of death from trauma for preschool-age children. The causes of drowning deaths vary with age and geographic area. In young children, bathtub and swimming pool drowning predominate, whereas in older children and adolescents, drowning occurs predominantly in natural bodies of water while the victim is swimming or boating.

Fire and burn deaths account for 8% of all unintentional trauma deaths and 14% in those younger than 5yr of age (see Chapter 75).

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**Table 5-1 Injury Deaths in the United States, 2010 [N (Rate per 100,000)]**

<table>
<thead>
<tr>
<th>CAUSE OF DEATH</th>
<th>YOUNGER THAN 1Yr</th>
<th>1-4 Yr</th>
<th>5-9 Yr</th>
<th>10-14 Yr</th>
<th>15-19 Yr</th>
<th>0-19 Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL CAUSES</td>
<td>24,586 (623.35)</td>
<td>4316 (26.55)</td>
<td>2330 (11.45)</td>
<td>2949 (14.26)</td>
<td>10887 (49.40)</td>
<td>45068 (10.43)</td>
</tr>
<tr>
<td>ALL INJURIES</td>
<td>1529 (38.77)</td>
<td>1862 (11.45)</td>
<td>905 (4.45)</td>
<td>1341 (6.49)</td>
<td>8182 (37.12)</td>
<td>13819 (16.60)</td>
</tr>
<tr>
<td>All unintentional*</td>
<td>1110 (28.14)</td>
<td>1264 (7.78)</td>
<td>758 (3.73)</td>
<td>885 (4.28)</td>
<td>4537 (20.58)</td>
<td>8684 (10.43)</td>
</tr>
<tr>
<td>Motor vehicle occupant</td>
<td>22 (0.56)</td>
<td>95 (0.58)</td>
<td>116 (0.57)</td>
<td>143 (0.69)</td>
<td>1065 (4.83)</td>
<td>1441 (1.73)</td>
</tr>
<tr>
<td>Pedestrian</td>
<td>12 (0.30)</td>
<td>206 (1.27)</td>
<td>96 (0.47)</td>
<td>115 (0.56)</td>
<td>315 (1.43)</td>
<td>744 (0.89)</td>
</tr>
<tr>
<td>Drowning</td>
<td>39 (0.99)</td>
<td>436 (2.68)</td>
<td>134 (0.66)</td>
<td>117 (0.57)</td>
<td>301 (1.37)</td>
<td>1027 (1.23)</td>
</tr>
<tr>
<td>Fire and burn</td>
<td>411 (0.04)</td>
<td>281 (1.73)</td>
<td>174 (0.86)</td>
<td>89 (0.47)</td>
<td>102 (0.46)</td>
<td>687 (0.83)</td>
</tr>
<tr>
<td>Poisoning</td>
<td>25 (0.63)</td>
<td>65 (0.40)</td>
<td>21 (0.10)</td>
<td>58 (0.28)</td>
<td>938 (4.26)</td>
<td>1107 (1.33)</td>
</tr>
<tr>
<td>Bicycle</td>
<td>0</td>
<td>2 (0.01)</td>
<td>17 (0.08)</td>
<td>39 (0.19)</td>
<td>54 (0.25)</td>
<td>112 (0.13)</td>
</tr>
<tr>
<td>Firearm</td>
<td>11 (0.28)</td>
<td>71 (0.44)</td>
<td>73 (0.36)</td>
<td>225 (1.09)</td>
<td>2331 (10.58)</td>
<td>2711 (3.26)</td>
</tr>
<tr>
<td>Fall</td>
<td>12 (0.30)</td>
<td>25 (0.15)</td>
<td>12 (0.06)</td>
<td>20 (0.10)</td>
<td>108 (0.49)</td>
<td>177 (0.21)</td>
</tr>
<tr>
<td>Suffocation</td>
<td>959 (24.31)</td>
<td>165 (1.02)</td>
<td>51 (0.25)</td>
<td>239 (1.16)</td>
<td>842 (3.82)</td>
<td>2256 (2.71)</td>
</tr>
<tr>
<td>All intentional</td>
<td>311 (7.89)</td>
<td>386 (2.37)</td>
<td>118 (0.58)</td>
<td>418 (2.02)</td>
<td>3508 (15.92)</td>
<td>4741 (5.69)</td>
</tr>
<tr>
<td>Suicide</td>
<td>0</td>
<td>0</td>
<td>7 (0.03)</td>
<td>267 (1.29)</td>
<td>1659 (7.53)</td>
<td>1933 (2.32)</td>
</tr>
<tr>
<td>Firearm suicide</td>
<td>0</td>
<td>0</td>
<td>80 (0.39)</td>
<td>688 (3.03)</td>
<td>749 (0.90)</td>
<td>749 (0.90)</td>
</tr>
<tr>
<td>Homicide</td>
<td>311 (7.89)</td>
<td>385 (2.37)</td>
<td>111 (0.55)</td>
<td>150 (0.73)</td>
<td>1832 (8.31)</td>
<td>2789 (3.35)</td>
</tr>
<tr>
<td>Firearm homicide</td>
<td>11 (0.28)</td>
<td>43 (0.26)</td>
<td>58 (0.29)</td>
<td>107 (0.52)</td>
<td>1554 (7.05)</td>
<td>1773 (2.13)</td>
</tr>
<tr>
<td>Undetermined intent</td>
<td>108 (2.74)</td>
<td>82 (0.50)</td>
<td>29 (0.14)</td>
<td>38 (0.18)</td>
<td>137 (0.62)</td>
<td>394 (0.47)</td>
</tr>
</tbody>
</table>


Most of these are a result of house fires; deaths are caused by smoke inhalation and asphyxiation rather than severe burns. Children and the elderly are at greatest risk for these deaths because of difficulty in escaping from burning buildings.

Suffocation accounts for approximately 86% of all unintentional deaths in children younger than 1 yr of age. The majority of these deaths result from choking on food items, such as hot dogs, candy, grapes, and nuts. Nonfood items that can cause choking include undersize infant pacifiers, small balls, and latex balloons. However, some of these deaths may represent misclassification of children dying from sudden infant death syndrome (see Chapter 37).

Homicide is the third leading cause of injury death in children 1-4 yr of age and the second leading cause of injury death in adolescents (15-19 yr old). Homicide in the pediatric age group falls into 2 patterns: infantile and adolescent. Child homicide involves children younger than age 5 yr and represents child abuse (see Chapter 40). The perpetrator is usually a caretaker; death is generally the result of blunt trauma to the head and/or abdomen. The adolescent pattern of homicide involves peers and acquaintances and is caused by firearms in 85% of cases. The majority of these deaths involve handguns. Children between these 2 age groups experience homicides of both types.

Suicide is rare in children younger than age 10 yr; only 1% of all suicides occur in children younger than age 15 yr. The suicide rate increases markedly after the age of 10 yr, with the result that suicide is now the third leading cause of death for 15-19 yr olds. Native American teenagers are at the highest risk, followed by white males; black females have the lowest rate of suicide in this age group. Approximately 40% of teen suicides involve firearms (see Chapter 27).

In the last decade, there has been a substantial increase in unintentional poisoning deaths among teens and young adults; in 2010 unintentional poisonings were the third leading cause of injury deaths among 15-24 year olds. Many of these were from prescription analgesic and opioid medications.

Nonfatal Injuries

Most childhood injuries do not result in death. Approximately 12% of children and adolescents receive medical care for an injury each year in hospital emergency departments, and at least an equal number are treated in physicians’ offices. Of these, 2% require inpatient care and 55% have at least short-term temporary disability as a result of their injuries.

The distribution of these nonfatal injuries is very different from that of fatal trauma (Fig. 5-3). Falls are the leading cause of both emergency department visits and hospitalizations. Bicycle-related trauma is the most common type of sports and recreational injury, accounting for approximately 300,000 emergency department visits annually. Nonfatal injuries, such as anoxic encephalopathy from near-drowning, scarring and disfigurement from burns, and persistent neurologic deficits from head injury, may be associated with severe morbidity, leading to substantial changes in the quality of life for victims and their families.

Global Child Injuries

Child injuries are a global public health issue and prevention efforts are necessary in low-, middle-, and high-income countries. Between 1990 and 2010 there was a 53% decrease in death rates of people of all ages from communicable, maternal, neonatal, and nutritional disorders whereas injury mortality rates decreased by only 16%. Worldwide, nearly 1 million children and adolescents die from injuries and violence each year, and more than 90% of these deaths are in low- and middle-income countries. As child mortality undergoes an epidemiologic transition because of better control of infectious diseases and malnutrition, injuries have and will increasingly become the leading cause of death for children in the developing world as it now is in all industrialized countries. Drowning is now the 5th most common cause of death for 5-9 yr old children globally, and in some countries, such as Bangladesh, it is the leading cause of death among children beyond the first year of life, with a rate 22 times greater than that in the Americas. An estimated 1 billion people do not currently have access to roads; as industrialization and motorization spreads, the incidence of motor vehicle crashes, injuries, and fatalities will climb. The rate of child injury death in low- and middle-income countries is 3-fold higher than that in high-income countries, and reflects both a higher incidence of many types of injuries as well as a much higher case-fatality ratio in those injured because of a lack of emergency and surgical care. As in high-income countries, prevention of child injuries and consequent morbidity and mortality is feasible with multifaceted approaches, many of which are low cost and of proven effectiveness.

PRINCIPLES OF INJURY CONTROL

Injury prevention once centered on attempts to pinpoint the innate characteristics of a child that result in greater frequency of injury. Most discount the theory of the accident-prone child. Although longitudinal studies have demonstrated an association between hyperactivity and impulsivity and increased rates of injury, the sensitivity and specificity of these traits for injury are extremely low. The concept of accident proneness is counterproductive in that it shifts attention away from potentially more modifiable factors, such as product design or the environment. It is more appropriate to examine the physical and social environment of children with frequent rates of injury than to try to identify particular personality traits or temperaments, which are difficult to modify. Children at high risk for injury are likely to be relatively poorly supervised, to have disorganized or stressed families, and to live in hazardous environments.

Efforts to control injuries include education or persuasion, changes in product design, and modification of the social and physical environment. Efforts to persuade individuals, particularly parents, to change their behaviors have constituted the greater part of injury control efforts. Speaking with parents specifically about using child car-seat restraints and bicycle helmets, installing smoke detectors, and checking the tap water temperature is likely to be more successful than offering well-meaning but too-general advice about supervising the child closely, being careful, and “childproofing” the home. This information should be geared to the developmental stage of the child and presented in moderate doses in the form of anticipatory guidance at well-child visits. Table 5-2 lists important topics to discuss at each developmental stage.

The most successful injury-prevention strategies generally are those involving changes in product design. These passive interventions protect all individuals in the population, regardless of cooperation or level of skill, and are likely to be more successful than active measures that require repeated behavior change by the parent or child. For some types of injuries, effective passive interventions are not available or feasible; we must rely heavily on attempts to change the behavior of individuals. The most important and effective product changes have been in motor vehicles. Turning down the water heater temperature,
from drowning and burns, and the new risk of intentional trauma. Work-related injuries associated with child labor, especially for 14-16 yr olds, are an additional risk.

Injuries occurring at a particular age represent a window of vulnerability during which a child or an adolescent encounters a new task or hazard that the adolescent may not have the developmental skills to handle successfully. Toddlers do not have the judgment to know that medications can be poisonous or that some houseplants are not to be eaten; they do not understand the hazard presented by a swimming pool or an open second-story window. For young children, parents may inadvertently set up this mismatch between the skills of the child and the demands of the task. Many parents expect young school-age children to walk home from school, the playground, or the local convenience store, tasks for which most children are not developmentally ready. Likewise, the lack of skills and experience to handle many tasks during the teenage years contributes to an increased risk of injuries, particularly motor vehicle injuries. The high rate of motor vehicle crashes among 15-17 yr old teens is caused in part by inexperience, but also appears to reflect their level of development and maturity. Alcohol, other drugs, and mobile phone use substantially add to these limitations.

Age also influences the severity of injury and the risk of long-term disability. Young school-age children have an incompletely developed pelvis. In a motor vehicle crash, the seatbelt does not anchor onto the pelvis, but rides up onto the abdomen, resulting in the risk of serious abdominal injury. Age also interacts with vehicle characteristics in that most children ride in the rear seat, which in the past was equipped only with lap belts and not with lap-shoulder harnesses. Proper restraint for 4-8 yr old children requires the use of booster seats. Children younger than the age of 2 yr have much poorer outcomes from traumatic brain injuries than do older children and adolescents.

**Gender**

Beginning at 1-2 yr of age and continuing throughout the life span, males have higher rates of fatal injury than females. During childhood, this does not appear to be primarily a result of developmental differences between the sexes, differences in coordination, or differences in muscle strength. Variation in exposure to risk may account for the male predominance in some types of injuries. Although boys in all age groups have higher rates of bicycle-related injuries, adjusting for exposure reduces this excess rate. Boys may have higher rates of injuries because they use bicycles more frequently or for more hours. Sex differences in rates of pedestrian injuries do not appear to be caused by differences in the amount of walking, but rather reflect differences in behavior between young girls and boys. Greater risk-taking behavior, combined with greater frequency of alcohol use, may lead to the disproportionately high rate of motor vehicle crashes among teenage males. The rate of violence related injuries is higher among males because of their risk-taking behavior.

**Race and Ethnicity**

Native Americans have the highest death rate from unintentional injuries. African-American children and adolescents have higher rates of fatal injuries than whites, whereas Asians have lower rates; rates for Hispanic children and adolescents are intermediate between those for African-Americans and those for whites. These discrepancies are even more pronounced for some injuries. The homicide rate for African-Americans age 15-19 yr was 29.6/100,000 in 2010, compared with 6.4/100,000 for American Indians and Alaskan Natives and 4.0/100,000 for whites and 2.0/100,000 for Asians. The suicide rate for Native American youth was 2.2 times the rate for whites and 4.4-fold greater than that for African-Americans. The rate of firearm homicide deaths for African-American youth ages 15-19 is nearly 9-fold higher than that for whites and 21 times that of Asian American youth.

These disparities appear to be primarily related to poverty, the educational status of parents, and the presence of hazardous environments. Homicide rates among African-Americans are nearly equivalent to those among whites, when adjusted for socioeconomic status. It is important to understand racial disparities in injury rates, but...
inappropriate to ascribe the etiology of these differences to race or ethnicity.

**Socioeconomic Status**

Poverty is one of the most important risk factors for childhood injury. Mortality from fires, motor vehicle crashes, and drowning is 2-4 times higher in poor children. Death rates among both African-Americans and whites have an inverse relationship to income level: the higher the income level, the lower the death rate. Native Americans have especially high rates. Other factors are single-parent families, teenage mothers, multiple care providers, family stress, and multiple siblings; these are primarily a function of poverty rather than independent risk factors.

**Rural–Urban Location**

Injury rates are generally higher in rural than in urban areas. Homicide rates are higher in urban areas, as is violent crime in general. Case fatality from injury is generally twice as high in rural areas than in urban areas, reflecting both the increased severity of some injuries (such as motor vehicle crashes occurring at higher speeds) and poorer access to emergency medical services and definitive trauma care in rural areas. Some injuries are unique to rural areas, such as agricultural injuries to children and adolescents.

**Environment**

Poverty increases the risk of injury to children, at least in part through its effect on the environment. Children who are poor are at increased risk for injury because they are exposed to more hazards in their living environments. They may live in poor housing, which is more likely to be dilapidated and less likely to be protected by smoke detectors. The roads in their neighborhoods are more likely to be major thoroughfares. Their neighborhoods are more likely to experience higher levels of violence, and they are more likely to be victims of assault than are children and adolescents living in the suburbs. The focus on the environment is also important because it directs attention away from relatively immutable factors, such as family dynamics, poverty, and race, and directs efforts toward factors that can be changed through interventions.

**MECHANISMS OF INJURY**

**Motor Vehicle Injuries**

Motor vehicle injuries are the leading cause of serious and fatal injuries for children and adolescents. Large and sustained reductions in motor vehicle crash injuries can be accomplished by identifiable interventions.

**Occupants**

Injuries to passenger vehicle occupants are the predominant cause of motor vehicle deaths among children and adolescents. The peak injury and death rate for both males and females in the pediatric age group occurs between 15 and 19 yr of age (see Table 5-1). Proper restraint use in vehicles is the single most effective method for preventing serious or fatal injury. Table 5-3 shows the recommended restraints at different ages. Figure 5-4 provides examples of car safety seats.

A detailed guide and list of acceptable devices is available from the AAP (http://www.healthychildren.org/english/safety-prevention/on-the-go/pages/car-safety-seats-information-for-families.aspx) and the National Highway Traffic Safety Administration (http://www.safecar.gov/parents/carseats.htm). Children weighing < 20 lb may use an infant seat or be placed in a convertible infant-toddler child-restraint device. Infants and toddlers younger than 1 to 2 yr or if less than manufacturer's weight limit should be placed in the rear seat facing backward; older toddlers and young children can be placed in the rear seat in a forward-facing child harness seat until it is outgrown. Emphasis must be placed on the correct use of these seats, including placing the seat in the right direction, routing the belt properly, and ensuring that the child is buckled into the seat correctly. Government regulations have made the fit between car seats and the car easier, quicker, and less prone to error. Children younger than age 13 yr should never sit in the front seat. Inflating airbags can be lethal to infants in rear-facing seats and to small children in the front passenger seat.

Older children are often not adequately restrained. Many children ride in the rear seat restrained with lap belts only. Booster seats have been shown to decrease the risk of injury by 59%, and should be used by children who are between 40 lb (=4 yr of age) and 80 lb, are <8 yr of age, and are <4 ft 9 in (145 cm) tall. Many states have extended their car seat laws to include children of booster seat age as well. Shoulder straps placed behind the child or under the arm do not provide adequate crash protection and may increase the risk of serious injury. The use of lap belts alone has been associated an increased risk of seatbelt-related injuries, especially fractures of the lumbar spine and hollow visceral injuries of the abdomen. These flexion-distraction injuries of the spine are usually accompanied by injuries to the abdominal organs.

The rear seat is clearly much safer than the front seat for both children and adults. One study of children younger than the age of 15 yr found that the risk of injury in a crash was 70% lower for children in the rear seat compared with those sitting in the front seat. Frontal

### Table 5-3  Recommended Child Restraint Methods

<table>
<thead>
<tr>
<th></th>
<th>INFANTS</th>
<th>TODDLERS (1-3)</th>
<th>YOUNG CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended age/weight requirements</strong></td>
<td>Birth to 1 yr or below weight limit of seat</td>
<td>Older than 1 yr and 20-40 lb</td>
<td>40-80 lb and under 4’9” in height; generally between 4 and 8 yr of age</td>
</tr>
<tr>
<td><strong>Type of seat</strong></td>
<td>Infant only or rear-facing convertible</td>
<td>Convertible or forward-facing harness seat</td>
<td>Belt positioning booster seat</td>
</tr>
<tr>
<td><strong>Seat position</strong></td>
<td>Rear-facing only. Place in back seat of vehicle</td>
<td>Can be rear-facing until 30 lb if seat allows; generally forward-facing. Place in back seat of vehicle</td>
<td>Forward-facing. Place in back seat of vehicle</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Children should use rear-facing seat until at least 1 yr and at least 20 lb</td>
<td>Harness straps should be at or above shoulder level</td>
<td>Belt positioning booster seats must be used with both lap and shoulder belts</td>
</tr>
<tr>
<td></td>
<td>Harness straps should be at or below shoulder level</td>
<td>Most seats require top strap for forward-facing use</td>
<td>Make sure the lap belt fits low and tightly across the lap/upper thigh area and the shoulder belt fits snugly, crossing the chest and shoulder to avoid abdominal injuries</td>
</tr>
</tbody>
</table>

Data from [http://www.safercar.gov/parents/CarSeats.htm](http://www.safercar.gov/parents/CarSeats.htm).
Drivers 15-17 yr of age have more than twice the rate of collisions compared with motorists 18 yr of age and older. Formal driver education courses for young drivers appear to be ineffective as a primary means of decreasing the number of collisions, and in fact may increase risk by allowing younger teens to drive. The risk of serious injury and mortality is directly related to the speed at the time of the crash and inversely related to the size of the vehicle. Small, fast cars greatly increase the risk of a fatal outcome in the event of a crash.

The number of passengers traveling with teen drivers influences the risk of a crash. The risk of death for 17 yr old drivers is 50% greater when driving with 1 passenger compared with driving alone; this risk is 2.6-fold higher with 2 passengers and 3-fold higher with 3 or more passengers. The risk is also increased if the driver is male and the passengers are younger than age 30 yr.

Teens driving at night are overrepresented in crashes and fatal crashes, with nighttime crashes accounting for >33% of teen motor vehicle fatalities. Almost 50% of fatal crashes involving drivers younger than age 18 yr occur in the 4 hr before or after midnight. Teens are 5-10 times more likely to be in a fatal crash while driving at night compared with driving during the day. The difficulty of driving at night combined with the inexperience of teen drivers appears to be a deadly combination.

Another risk factor for motor vehicle crashes for people of all ages, including teens, is distracted driving from the use of mobile devices for texting or talking. In 2011, 3/4 of high school students reported they had texted or emailed while driving in the last 30 days. Dialing on a cell phone increases the risk of a crash nearly 3-fold, and texting may increase the risk as much as 6-fold. Although 44 states have banned text messaging for all drivers, the effect of state laws on prohibiting such behavior well driving is unknown. Parents should set limits on the use of these devices by their teens; technological interventions that can block cell phone signals in a moving vehicle may also be available.

**Graduated licensing laws (GLLs)** consist of a series of steps over a designated period before a teen can get full, unrestricted driving privileges. In a 3-stage graduated license, the student driver must first pass vision and knowledge-based tests. This is followed by obtaining a learner’s permit and once a specific age has been achieved and driving skills advanced, the student driver is eligible to take the driving test. Once given the provisional license, the new driver will have a specified time to do low-risk driving. GLLs usually place initial restrictions on the number of passengers (especially teenaged) allowed in the vehicle and restrict driving during nighttime. There is a decrease in the number of crashes of 10-30% among the youngest drivers in states with a GLL system. The characteristics of GLLs vary substantially across states.

Alcohol use is a major cause of motor vehicle trauma among adolescents. The combination of inexperience in driving and inexperience with alcohol is particularly dangerous. Approximately 20% of all deaths from motor vehicle crashes in this age group are the result of alcohol intoxication, with impairment of driving seen at blood alcohol concentrations as low as 0.05 g/dL. Approximately 30% of adolescents report riding with a driver who had been drinking and approximately 10% report driving after drinking. All states have adopted a zero tolerance policy, which defines any measurable alcohol content as legal intoxication, to adolescent drinking while driving. All adolescent motor vehicle injury victims should have their blood alcohol concentration measured in the emergency department and be screened for high-risk alcohol use with a validated screening test (such as the CRAFFT or Alcohol Use Disorders Identification Test [AUDIT] screening tools) to identify those with alcohol abuse problems (see Chapter 114.1). Individuals who have evidence of alcohol abuse should not leave the emergency department or hospital without plans for appropriate alcohol abuse treatment. Interventions for problem drinking can be effective in decreasing the risk of subsequent motor vehicle crashes. Even brief interventions in the emergency department using motivational interviewing can be successful in decreasing adolescent problem drinking.

Another cause of impaired driving is marijuana use. In 2011, nearly one-quarter of high school students reported using marijuana in the prior 30 days. Marijuana use doubles the risk of a crash; as with alcohol,
this effect may be more pronounced with less experienced drivers. As of this writing, two states (Washington and Colorado) have legalized the sale of marijuana for adults; the effects of this on adolescent injury remains to be determined.

**All-Terrain Vehicles.** All-terrain vehicles (ATVs) in many parts of the country are an important cause of injuries to children and adolescents. These vehicles can attain high speeds and are prone to rollover because of their high center of gravity. Orthopedic and head injuries are the most common serious injuries seen among children involved in ATV crashes. Helmets can significantly decrease the risk and severity of head injuries among ATV riders, but current use is very low. Voluntary industry efforts to decrease the risk of injuries appear to have had little effect in making ATVs safer. The AAP recommends that children younger than 16 yr of age should not ride on ATVs.

**Bicycle Injuries.** Each year in the United States, approximately 300,000 children and adolescents are treated in emergency departments for bicycle-related injuries, making this one of the most common reasons that children with trauma visit emergency departments. The majority of severe and fatal bicycle injuries involve head trauma. A logical step in the prevention of these head injuries is the use of helmets. Helmets are very effective, reducing the risk of all head injury by 85% and the risk of traumatic brain injury by 88%. Helmets also reduce injuries to the mid and upper face by as much as 65%. Pediatricians can be effective advocates for the use of bicycle helmets and should incorporate this advice into their anticipatory guidance schedules for parents and children. Appropriate helmets are those with a firm polystyrene liner that fit properly on the child’s head. Parents should avoid buying a larger helmet to give the child a “growing room.”

Promotion of helmet use can and should be extended beyond the pediatrician’s office. Community education programs spearheaded by coalitions of physicians, educators, bicycle clubs, and community service organizations have been successful in promoting the use of bicycle helmets to children across the socioeconomic spectrum, resulting in helmet use rates of 60% or more with a concomitant reduction in the number of head injuries. Passage of bicycle helmet laws also leads to increased helmet use.

Consideration should also be given to other types of preventive activities, although the evidence supporting their effectiveness is limited. Bicycle paths are a logical method for separating bicycles and motor vehicles.

**Pedestrian Injuries.** Pedestrian injuries are an important cause of traumatic death for children and adolescents in the United States and in most high-income countries. In low-income countries, a much higher proportion of motor vehicle fatalities are pedestrians, especially among 5-14 yr old old. Although case fatality rates are ≤5%, serious nonfatal injuries constitute a much larger problem, resulting in 60,000 emergency department visits annually for children and adolescents. Pedestrian injuries are the most important cause of traumatic coma in children and a frequent cause of serious lower extremity fractures, particularly in school-age children.

Most injuries occur during the day, with a peak in the after-school period. Improved lighting or reflective clothing would be expected to prevent few injuries. Surprisingly, approximately 30% of pedestrian injuries occur while the individual is in a marked crosswalk, perhaps reflecting a false sense of security and decreased vigilance in these areas. The risk of pedestrian injury is greater in neighborhoods with high traffic volumes, speeds greater than ~25 mph, absence of play space adjacent to the home, household crowding, and low socioeconomic status.

One important risk factor for childhood pedestrian injuries is the developmental level of the child. Children < 5 yr are at risk for being run over in the driveway. Few children < 9 or 10 yr of age have the developmental skills to successfully negotiate traffic 100% of the time. Young children have poor ability to judge the distance and speed of traffic and are easily distracted by playmates or other factors in the environment. Many parents are not aware of this potential mismatch between the abilities of the young school-age child and the skills needed to cross streets safely. The use of mobile phones and devices has become increasingly common while walking, and can increase the risk of being struck by a motor vehicle.

Prevention of pedestrian injuries is difficult, but should consist of a multifaceted approach. Education of the child in pedestrian safety should be initiated at an early age by the parents and continue into the school-age years. Younger children should be taught never to cross streets when alone; older children should be taught (and practice how) to negotiate quiet streets with little traffic. Major streets should not be crossed alone until the child is at least 10 yr of age or older and has been observed to follow safe practices.

Legislation and police enforcement are important components of any campaign to reduce pedestrian injuries. Right-turn-on-red laws increase the hazard to pedestrians. In many cities, few drivers stop for pedestrians in crosswalks, a special hazard for young children. Engineering changes in roadway design are extremely important as passive prevention measures. Most important are measures to slow the speed of traffic and to route traffic away from schools and residential areas; these efforts are endorsed by parents and can decrease the risk of injuries and death by 10-35%. Other modifications include networks of 1-way streets, proper placement of transit or school bus stops, sidewalks in urban and suburban areas, edge striping in rural areas to delineate the edge of the road, and curb parking regulations. Comprehensive traffic “calming” schemes using these strategies have been very successful in reducing child pedestrian injuries in Sweden, the Netherlands, Germany, and increasingly, the United States.

**Ski- and Snowboard-Related Head Injuries.** The increasing use of helmets in snow sports, such as skiing and snowboarding, is encouraging. Since head injuries are the most common cause of death in these sports, and helmets reduce the risk of head injury by 50% or more. Use of helmets does not result in skiers or snowboarders taking more risks and should be encouraged in all snow sports.

**Fire- and Burn-Related Injuries.** See Chapter 75.

**Poisoning.** See Chapter 63.

**Drowning.** See Chapter 74.

**Traumatic Brain Injury.** See Chapter 68.

**Firearm Injuries.** Injuries to children and adolescents involving firearms occur in 3 different situations: unintentional injury, suicide attempt, and assault. The injury induced may be fatal or may result in permanent sequelae.

Unintentional firearm injuries and deaths have continued to decrease and accounted for 134 deaths in 2010, representing only a very small fraction of all firearm injuries among children and adolescents. The majority of these deaths occur to teens during hunting or recreational activities. Suicide is the third most common cause of death from all causes in both males and females ages 10-19 yr. During the 1950s to 1970s, suicide rates for children and adolescents more than doubled; firearm suicide rates peaked in 1994 and decreased by 59% from this peak by 2010. The difference in the rate of suicide death between males and females is related to the differences in method used during attempts. Women die less often in suicide attempts, partly because they use less-lethal means (mainly drugs) and perhaps have a lower degree of intent. The use of firearms in a suicidal act usually converts an attempt into a fatality.

Homicides are second only to motor vehicle crashes among causes of death in teenagers older than 15 yr. In 2010, 1,832 adolescents age 15-19 yr were homicide victims; African American teenagers accounted for 52% of the total, making homicides the most common cause of death among African-American teenagers. Hispanic teenagers accounted for nearly 17% of the homicide deaths in this age group. In 2010, 85% of homicides among teenage males involved firearms, the majority of which are handguns.

In the United States, approximately 34% of households owned guns in 2012. Handguns account for approximately 30% of the firearms in use today; yet, they are involved in 80% of criminal and other firearm misuse. Home ownership of guns increases the risk of adolescent suicide 3- to 10-fold and the risk of adolescent homicide up to 4-fold. In homes with guns, the risk to the occupants is far greater than the chance that the gun will be used against an intruder; for every death
Adults who commit violent acts usually have a history of violent behavior during childhood or adolescence. Longitudinal studies following groups of individuals from birth have found that aggression occurs among infants and that most children learn to control this aggression early in childhood. Children who later become violent adolescents and adults do not learn to control this aggressive behavior.

The most successful interventions for violence target young children and their families. These include home visits by nurses and paraprofessionals beginning in the prenatal period and continuing for the first few years of life to provide support and guidance to parents, especially parents without other resources. Enrollment in early childhood education programs (e.g. Head Start) starting at age 3 yr has been shown to be effective in improving school success, keeping children in school, and decreasing the chance that the child will be a delinquent adolescent. School-based interventions, including curricula to increase the social skills of children and improve the parenting skills of caregivers, have long-term effects on violence and risk-taking behavior. Early identification of behavior problems by primary care pediatricians can best be accomplished through the routine use of formal screening tools. Interventions in adolescence, such as family therapy, multisystemic therapy, and therapeutic foster care, can decrease problem behavior and a subsequent decline into delinquency and violence.

Psychosocial Consequences of Injuries

Many children and their parents have substantial psychosocial sequelae from trauma. Studies in adults indicate that 10–40% of hospitalized injured patients will have posttraumatic stress disorder (PTSD; see Chapter 25). Among injured children involved in motor vehicle crashes, 90% of families will have symptoms of acute stress disorder after the crash, although the diagnosis of acute stress disorder is not predictive of later PTSD. Standardized questionnaires that collect data from the child, the parents, and the medical record at the time of initial injury can serve as useful screening tests for later development of PTSD. Early mental health intervention, with close follow-up, is important for the treatment of PTSD and for minimizing its effect on the child and family.

Bibliography is available at Expert Consult.
Bibliography


The field of pediatrics is dedicated to optimizing the growth and development of each child. Pediatricians require knowledge of normal growth, development, and behavior in order to effectively monitor children’s progress, identify delays or abnormalities in development, obtain needed services, and counsel parents and caretakers. To alter factors that increase or decrease risk, pediatricians need to understand how biologic and social forces interact within the parent-child relationship, within the family, and between the family and the larger society. Growth is an indicator of overall well-being, status of chronic disease, and interpersonal and psychologic stress. By monitoring children and families over time, pediatricians are uniquely situated to observe the interrelationships between physical growth and cognitive, motor, and emotional development. Observation is enhanced by familiarity with developmental theory and understanding of developmental models which describe normal patterns of behavior and provide guidance for prevention of behavior problems.

BIOPSYCHOSOCIAL MODEL AND ECOBIODEVELOPMENTAL FRAMEWORK: MODELS OF DEVELOPMENT

The medical model presumes that a patient presents with signs and symptoms and a physician focuses on diagnosing and treating diseases of the body. This model neglects the psychologic aspect of a person who exists in the larger realm of the family and society. In the biopsychosocial model, higher-level systems are simultaneously considered with the lower-level systems that make up the person and the person’s environment (Fig. 6-1). A patient’s symptoms are examined and explained in the context of the patient’s existence. This basic model can be used to understand health and both acute and chronic disease.

With the advances in neurology, genomics including epigenetics, molecular biology and the social sciences, a more accurate model, the ecobiodevelopmental framework has emerged. This framework emphasizes how the ecology of childhood (social and physical environments) interacts with biologic processes to determine outcomes and life trajectories. Early influences, particularly those producing toxic levels of stress, affect the individual through modification of gene expression, without change in DNA sequencing. These epigenetic changes, such as DNA methylation and histone acetylation, are a result of environmental insults. Stress responses may produce alterations in brain structure and function, leading to disruption of later coping mechanisms. These changes will produce long-lasting effects on the health and well-being of the individual and may be passed on to future generations (Fig. 6-2).

Critical to learning and remembering (and therefore development) is neuronal plasticity, which permits the central nervous system to reorganize neuronal networks in response to environmental stimulation, both positive and negative. An overproduction of neuronal precursors eventually leads to about 100 billion neurons in the adult brain.

Each neuron develops on average 15,000 synapses by 3 yr of age. Synapses in frequently used pathways are preserved, whereas less-used ones atrophy through neuronal “pruning.” Changes in the strength and number of synapses and reorganization of neuronal circuits also play important roles in brain plasticity. Increases or decreases in synaptic activity result in persistent increases or decreases in synaptic strength. Thus experience (environment) has a direct effect on the physical and therefore functional properties of the brain (genetics). Children with different talents and temperaments (already a combination of genetics and environment) further elicit different stimuli from their (differing) environments.

Periods of behavioral development generally correlate with periods of great changes in synaptic numbers in relevant areas of the brain. Accordingly, sensory deprivation during the time when synaptic changes should be occurring has profound effects. The effects of strabismus leading to amblyopia in 1 eye may occur quickly during early childhood; likewise, patching the eye with good vision to reverse amblyopia in the other eye is less effective in late childhood (see Chapter 621). Early experience is particularly important because learning proceeds more efficiently along established synaptic pathways. Traumatic experiences also create enduring alterations in the neurotransmitter and endocrine systems that mediate the stress response, with effects noted later in life. Positive and negative experiences do not determine the total outcome, but shift the probabilities by influencing the child’s ability to respond adaptively to future stimuli. The plasticity of the brain continues into adolescence, with further development of the prefrontal cortex, which is important in decision-making, future planning, and emotional control; neurogenesis persists in adulthood in certain areas of the brain, including the subventricular zone of the lateral ventricles and in portions of the hippocampus.

Biologic Influences

Biologic influences on development include genetics, in utero exposure to teratogens, the long-term negative effects of low birthweight (neonatal morbidities plus increased rates of obesity, coronary heart disease, stroke, hypertension, and type 2 diabetes), postnatal illnesses, exposure to hazardous substances, and maturation. Adoption and twin studies consistently show that heredity accounts for approximately 40% of the variance in IQ and in other personality traits, such as sociability and desire for novelty, whereas shared environment accounts for another 50%. The negative effects on development of prenatal exposure to teratogens, such as mercury and alcohol, and of postnatal insults, such as meningitis and traumatic brain injury, have been extensively studied (see Chapters 96 and 99). Any chronic illness can affect growth and development, either directly or through changes in nutrition, parenting, or peer interactions.

The age at which children walk independently is similar around the world, despite great variability in child-rearing practices. The attainment of other skills, such as the use of complex sentences, is less tightly bound to a maturational schedule. Maturational changes also generate behavioral challenges at predictable times. Decrements in growth rate and sleep requirements around 2 yr of age often generate concern about poor appetite and refusal to nap. Although it is possible to accelerate many developmental milestones (toilet training a 12 mo old or teaching a 3 yr old to read), the long-term benefits of such precocious accomplishments are questionable.

In addition to physical changes in size, body proportions, and strength, maturation brings about hormonal changes. Sexual differentiation, both somatic and neurologic, begins in utero. Both stress and reproductive hormones affect brain development as well as behavior throughout development.
Temperament describes the stable, early-appearing individual variations in behavioral dimensions, including emotionality (crying, laughing, sulking), activity level, attention, sociability, and persistence. The classic theory proposes 9 dimensions of temperament (Table 6-1). These characteristics lead to 3 common constellations: (1) the easy, highly adaptable child, who has regular biologic cycles; (2) the difficult child, who withdraws from new stimuli and is easily frustrated; and (3) the slow-to-warm-up child, who needs extra time to adapt to new circumstances. Various combinations of these clusters also occur. Temperament has long been described as biologic or “inherited.” Monozygotic twins are rated by their parents as temperamentally similar more often than are dizygotic twins. Estimates of heritability suggest that genetic differences account for approximately 20-60% of the variability of temperament within a population. The remainder of the variance is attributed to the child’s environment. Maternal prenatal stress and anxiety is associated with child temperament, possibly through stress hormones. However, certain polymorphisms of specific genes moderate the influence of maternal stress on infant temperament (specifically irritability) illustrating the interplay between genes and environment. Longitudinal twin studies of adult personality indicate that changes in personality over time largely result from non-shared environmental influences, whereas stability of temperament appears to result from genetic factors.

The concept of temperament can help parents understand and accept the characteristics of their children without feeling responsible for having caused them. Children who have difficulty adjusting to change may have behavior problems when a new baby arrives or at the time of school entry. In addition, pointing out the child’s temperament may allow for adjustment in parenting styles. Behavioral and emotional problems may develop when the temperamental characteristics of children and parents are in conflict.

Psychologic Influences: Attachment and Contingency

The influence of the child-rearing environment dominates most current models of development. Infants in hospitals and orphanages, deprived of opportunities for attachment, have severe developmental deficits. Attachment refers to a biologically determined tendency of a young child to seek proximity to the parent during times of stress and also to the relationship that allows securely attached children to use

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**Figure 6-1** Continuum and hierarchy of natural systems in the biopsychosocial model. (From Engel GL: The clinical application of the biopsychosocial model, Am J Psychiatry 137:535–544, 1980.)

their parents to reestablish a sense of well-being after a stressful experience. Insecure attachment may be predictive of later behavioral and learning problems.

At all stages of development, children progress optimally when they have adult caregivers who pay attention to their verbal and nonverbal cues and respond accordingly. In early infancy, such contingent responsiveness to signs of overarousal or underarousal helps maintain infants in a state of quiet alertness and fosters autonomic self-regulation. **Contingent responses** (reinforcement depending on the behavior of the other) to nonverbal gestures create the groundwork for the shared attention and reciprocity that are critical for later language and social development. Children learn best when new challenges are just slightly harder than what they have already mastered, a degree of difficulty dubbed the “zone of proximal development.” Psychologic forces, such as attention problems (see Chapter 33) or mood disorders (see Chapter 26), will have profound effects on many aspects of an older child’s life.

**Social Factors: Family Systems and the Ecologic Model**

Contemporary models of child development recognize the critical importance of influences outside of the mother–child dyad. Fathers play critical roles, both in their direct relationships with their children and in supporting mothers. As traditional nuclear families become less dominant, the influence of other family members (grandparents, foster and adoptive parents, same-sex partners) becomes increasingly important. Children are increasingly raised by unrelated caregivers while parents work or while they are in foster care. Families function as systems, with internal and external boundaries, subsystems, roles, and rules for interaction. In families with rigidly defined parental subsystems, children may be denied any decision-making, exacerbating rebelliousness. In families with poorly defined parent–child boundaries, children may be required to take on responsibilities beyond their years, or may be recruited to play a spousal role.

**Family systems theory** recognizes that individuals within systems adopt implicit roles. One child may be the troublemaker, whereas another is the negotiator and another is quiet. Birth order may have profound effects on personality development, through its influence on family roles and patterns of interaction. Families are dynamic. Changes in one person’s behavior affect every other member of the system; roles shift until a new equilibrium is found. The birth of a new child, attainment of developmental milestones such as independent walking, the onset of nighttime fears, and the death of a grandparent are all changes that require renegotiation of roles within the family and have the potential for healthy adaptation or dysfunction.

The family system, in turn, functions within the larger systems of extended family, subculture, culture, and society. Bronfenbrenner’s ecologic model depicts these relationships as concentric circles, with the parent–child dyad at the center (with associated risks and protective factors) and the larger society at the periphery. Changes at any level are reflected in the levels above and below. The shift from an industrial economy to one based on service and information is an obvious example of societal change with profound effects on families and children.

**Unifying Concepts: The Transactional Model, Risk, and Resilience**

The transactional model proposes that a child’s status at any point in time is a function of the interaction between biologic and social influences. The influences are bidirectional: Biologic factors, such as temperament and health status, both affect the child-rearing environment and are affected by it. A premature infant may cry little and sleep for long periods; the infant’s depressed parent may welcome this good behavior, setting up a cycle that leads to poor nutrition and inadequate growth. The child’s failure to thrive may reinforce the parent’s sense of failure as a parent. At a later stage, impulsivity and inattention associated with early, prolonged undernutrition may lead to aggressive behavior. The cause of the aggression in this case is not the prematurity, the undernutrition, or the maternal depression, but the interaction of all these factors (Fig. 6-3). Conversely, children with biologic risk factors may nevertheless do well developmentally if the child-rearing environment is supportive. Premature infants with electroencephalographic evidence of neurologic immaturity may be at increased risk for cognitive delay. This risk may only be realized when the quality of parent–child interaction is poor. When parent–child interactions are optimal, prematurity carries a reduced risk of developmental disability.

Children growing up in poverty experience multiple levels of developmental risk: increased exposure to biologic risk factors, such as environmental lead and undernutrition, lack of stimulation in the home, and decreased access to interventional education and therapeutic experiences. As they respond by withdrawal or acting out, they further discourage positive stimulation from those around them.

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**Table 6-1** Temperamental Characteristics: Descriptions and Examples

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>DESCRIPTION</th>
<th>EXAMPLES*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity level</td>
<td>Amount of gross motor movement</td>
<td>“She’s constantly on the move.” “He would rather sit still than run around.”</td>
</tr>
<tr>
<td>Rhythmicity</td>
<td>Regularity of biologic cycles</td>
<td>“He’s never hungry at the same time each day.” “You could set a watch by her nap.”</td>
</tr>
<tr>
<td>Approach and withdrawal</td>
<td>Initial response to new stimuli</td>
<td>“She rejects every new food at first.” “He sleeps well in any place.”</td>
</tr>
<tr>
<td>Adaptability</td>
<td>Ease of adaptation to novel stimulus</td>
<td>“Changes upset him.” “She adjusts to new people quickly.”</td>
</tr>
<tr>
<td>Threshold of responsiveness</td>
<td>Intensity of stimuli needed to evoke a response (e.g., touch, sound, light)</td>
<td>“He notices all the lumps in his food and objects to them.” “She will eat anything, wear anything, do anything.”</td>
</tr>
<tr>
<td>Intensity of reaction</td>
<td>Energy level of response</td>
<td>“She shouts when she is happy and wails when she is sad.” “He never cries much.”</td>
</tr>
<tr>
<td>Quality of mood</td>
<td>Usual disposition (e.g., pleasant, glum)</td>
<td>“He does not laugh much.” “It seems like she is always happy.”</td>
</tr>
<tr>
<td>Distractibility</td>
<td>How easily diverted from ongoing activity</td>
<td>“She is distracted at mealtimes when other children are nearby.” “He doesn’t even hear me when he is playing.”</td>
</tr>
<tr>
<td>Attention span and persistence</td>
<td>How long a child pays attention and sticks with difficult tasks</td>
<td>“He goes from toy to toy every minute.” “She will keep at a puzzle until she has mastered it.”</td>
</tr>
</tbody>
</table>

*Typical statements of parents, reflecting the range for each characteristic from very little to very much.
Children of adolescent mothers are also at risk. When early intervention programs provide timely, intensive, comprehensive, and prolonged services, at-risk children show marked and sustained upswings in their developmental trajectory. Early identification of children at developmental risk, along with early intervention to support parenting, is critically important.

An estimate of developmental risk can begin with a tally of risk factors, such as low income, limited parental education, and lack of neighborhood resources. There is a direct relationship between developmental outcome at age 13 yr and the number of social and family risk factors at age 4 yr (Fig. 6-4). Both individual stress and community-level poverty and disorder are associated with shortened telomeres in salivary samples, a link to health disparities. Protective (resilience) factors must also be considered. These factors, like risk factors, may be either biologic (temperamental persistence, athletic talent) or social. The personal histories of children who overcome poverty often include either biologic (temperamental persistence, athletic talent) or social.

**Developmental Domains and Theories of Emotion and Cognition**

Child development can also be tracked by the child’s developmental progress in particular domains, such as gross motor, fine motor, social, emotional, language, and cognition. Within each of these categories are developmental lines or sequences of changes leading up to particular attainments. Developmental lines in the gross motor domain, leading from rolling to creeping to independent walking, are obvious. Others, such as the line leading to the development of conscience, are more subtle.

The concept of a developmental line implies that a child passes through successive stages. Several psychoanalytic theories are based on stages as qualitatively different epochs in the development of emotion and cognition (Table 6-2). In contrast, behavioral theories rely less on qualitative change and more on the gradual modification of behavior and accumulation of competence.

**Psychoanalytic Theories**

At the core of Freudian theory is the idea of body-centered (or, broadly, “sexual”) drives; the emotional health of both the child and the adult depends on adequate resolution of these conflicts. Although Freudian ideas have been challenged, they opened the door to subsequent theories of development.

Erikson recast Freud's stages in terms of the emerging personality (see Table 6-2). The child’s sense of basic trust develops through the successful negotiation of infantile needs. As children progress through these psychosocial stages, different issues become salient. It is predictable that a toddler will be preoccupied with establishing a sense of autonomy; whereas a late adolescent may be more focused on establishing meaningful relationships and an occupational identity. Erikson recognized that these stages arise in the context of Western European societal expectations; in other cultures, the salient issues may be quite different.

Erikson’s work calls attention to the intrapersonal challenges facing children at different ages in a way that facilitates professional intervention. Knowing that the salient issue for school-age children is industry vs inferiority, pediatricians inquire about a child’s experiences of mastery and failure and (if necessary) suggest ways to ensure adequate successes.

**Cognitive Theories**

Cognitive development is best understood through the work of Piaget. A central tenet of Piaget’s work is that cognition changes in quality, not just quantity (see Table 6-2). During the sensorimotor stage, an infant's thinking is tied to immediate sensations and a child's ability to manipulate objects. The concept of “in” is embodied in a child’s act of putting a block into a cup. With the arrival of language, the nature of thinking changes dramatically; symbols increasingly take the place of objects and actions. Piaget described how children actively construct knowledge for themselves through the linked processes of assimilation (taking in new experiences according to existing schemata) and accommodation (creating new patterns of understanding to adapt to new information). In this way, children are continually and actively reorganizing cognitive processes.
Piaget's basic concepts have held up well. Challenges have included questions about the timing of various stages and the extent to which context may affect conclusions about cognitive stage. Children's understanding of cause and effect may be considerably more advanced in the context of sibling relationships than in the manipulation and perception of inanimate objects. In many children, logical thinking appears well before puberty, the age postulated by Piaget. Of undeniable importance is Piaget's focus on cognition as a subject of empirical study, the universality of the progression of cognitive stages, and the image of a child as actively and creatively interpreting the world.

Piaget's work is of special importance to pediatricians for 3 reasons: (1) Piaget's observations provide insight into many puzzling behaviors of infancy, such as the common exacerbation of sleep problems at 9 and 18 mo of age. (2) Piaget's observations often lend themselves to quick replication in the office, with little special equipment. (3) Open-ended questioning, based on Piaget's work, can provide insights into children's understanding of illness and hospitalization.

Based on cognitive development, Kohler developed a theory of moral development in 6 stages, from early childhood through adulthood. Preschoolers' earliest sense of right and wrong is egocentric, motivated by externally applied controls. In later stages, children perceive equality, fairness, and reciprocity in their understanding of interpersonal interactions through perspective-taking. Most youth will reach stage 4, conventional morality, by mid to late adolescence. The basic theory has been modified to distinguish morality from social conventions. Whereas moral thinking considers interpersonal interactions, justice, and human welfare, social conventions are the agreed-on standards of behavior particular to a social or cultural group. Within each stage of development, children are guided by the basic precepts of moral behavior, but also may take into account local standards, such as dress code, classroom behavior, and dating expectations. Additional studies have even demonstrated some moral equivalence in infants.

**Behavioral Theory**
This theoretical perspective distinguishes itself by its lack of concern with a child's inner experience. Its sole focus is on observable behaviors and measurable factors that either increase or decrease the frequency with which these behaviors occur. No stages are implied; children, adults, and, indeed, animals all respond in the same way. In its simplest form, the behaviorist orientation asserts that behaviors that are positively reinforced occur more frequently; behaviors that are negatively reinforced or ignored occur less frequently. The strengths of this position are its simplicity, wide applicability, and conduciveness to scientific verification. A behavioral approach lends itself to interventions for various common problems, such as temper tantrums, aggressive preschool behavior, and eating disorders in which behaviors are broken down into discrete units. In cognitively limited children and children with autism spectrum disorders (see Chapter 30), behavioral interventions using applied behavior analysis approaches have demonstrated their ability to teach new, complex behaviors. Applied behavior analysis has been particularly useful in the treatment of early-diagnosed autism (see Chapter 30.1). However, in cases in which misbehavior is symptomatic of an underlying emotional, perceptual, or family problem, an exclusive reliance on behavior therapy risks leaving the cause untreated. Behavioral approaches can be taught to parents to apply at home.

**Theories Commonly Employed in Behavioral Interventions**
An increasing number of programs or interventions (within and outside of the physician's office) are designed to influence behavior; some of these models are based on behavioral or cognitive theory or may have attributes of both. The most commonly employed models are the Health Belief Model, Theory of Reasoned Action, Theory of Planned Behavior, Social Cognitive Theory, and the Transtheoretical Model, which is also known as Stages of Change Theory. Pediatricians should be aware of these models; Table 6-3 shows the similarities and differences between these models. Interventions based on these theories have been designed for children and adolescents in community, clinic, and hospital-based settings.

**Motivational interviewing** is a technique often used in clinical settings to bring about behavior change, rather than a behavioral theory. The goal in using the technique is to enhance an individual's motivation to change behavior by exploring and removing ambivalence. This may be practiced by an individual practitioner and is taught in some pediatric residency programs. Motivational interviewing emphasizes the importance of the therapist (which may be a pediatrician, other physician, psychologist, social worker, etc.) understanding the client's perspective and displaying unconditional support. The therapist is a partner rather than an authority figure and recognizes that, ultimately, the patient has control over the patient's choices.

**Statistics Used in Describing Growth and Development**
(See Chapters 15 and 16.)

In everyday use, the term normal is synonymous with healthy. In a statistical sense, normal means that a set of values generates a normal (bell-shaped or gaussian) distribution. This is the case with anthropometric quantities, such as height and weight, and with many developmental milestones, such as the age of independent standing. For a normally distributed measurement, a histogram with the quantity (height, age) on the x-axis and the frequency (the number of children of that height, or the number who stand on their own at that age) on the y-axis generates a bell-shaped curve. In an ideal bell-shaped curve, the peak corresponds to the arithmetic mean (average) of the sample and to the median and the mode as well. The median is the value above and below which 50% of the observations lie; the mode is the value having the highest number of observations. Distributions are termed skewed if the mean, median, and mode are not the same number.

The extent to which observed values cluster near the mean determines the width of the bell and can be described mathematically by the standard deviation (SD). In the ideal normal curve, a range of values extending from 1 SD below the mean to 1 SD above the mean includes approximately 68% of the values, and each "tail" above and
<table>
<thead>
<tr>
<th>CONCEPT</th>
<th>GENERAL TENET OF THE CONCEPT “ENGAGING IN THE BEHAVIOR IS LIKELY IF ...”</th>
<th>HEALTH BELIEF MODEL</th>
<th>THEORY OF REASONED ACTION</th>
<th>THEORY OF PLANNED BEHAVIOR</th>
<th>SOCIAL COGNITIVE THEORY</th>
<th>TRANSTHEORETICAL MODEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATTITUdINAL BELIEFS</td>
<td>Appraisal of the positive and negative aspects of the behavior and expected outcome of the behavior</td>
<td>The positive aspects outweigh the negative aspects</td>
<td>Benefits, barriers/health motive</td>
<td>Behavioral beliefs and evaluation of those beliefs (attitudes)</td>
<td>Behavioral beliefs and evaluation of those beliefs (attitudes)</td>
<td>Outcome expectations/expectancies</td>
</tr>
<tr>
<td>SELF-EFFICACY BELIEFS/BELIEFS ABOUT CONTROL OVER THE BEHAVIOR</td>
<td>Belief in one’s ability to perform the behavior; confidence</td>
<td>One believes in their ability to perform the behavior</td>
<td>Self-efficacy</td>
<td>—</td>
<td>Perceived behavioral control</td>
<td>Self-efficacy</td>
</tr>
<tr>
<td>NORMATIVE AND NORM-RELATED BELIEFS AND ACTIVITIES</td>
<td>Belief that others want you to engage in the behavior (and one’s motivation to comply); may include actual support of others</td>
<td>One believes that people important to one want one to engage in the behavior; person has others’ support</td>
<td>Cues from media, friends (cues to action)</td>
<td>Normative beliefs and motivation to comply (subjective norms)</td>
<td>Normative beliefs and motivation to comply (subjective norms)</td>
<td>Social support</td>
</tr>
<tr>
<td>Belief that others (e.g., peers) are engaging in the behavior Responses to one’s behavior that increase or decrease the likelihood one will engage in the behavior; may include reminders</td>
<td>One believes that other people are engaging in the behavior One receives positive reinforcement from others or creates positive reinforcements for one’s self</td>
<td>—</td>
<td>Cues from media, friends (cues to action)</td>
<td>—</td>
<td>—</td>
<td>Social environment/norms; modeling Reinforcement</td>
</tr>
<tr>
<td>RISK-RELATED BELIEFS AND EMOTIONAL RESPONSES</td>
<td>Belief that one is at risk if one does not engage in the behavior, and that the consequences may be severe; may include actually experiencing negative emotions or symptoms and coping with them</td>
<td>One feels at risk with regard to a negative outcome or disease</td>
<td>Perceived susceptibility/severity (perceived threat)</td>
<td>—</td>
<td>—</td>
<td>Emotional coping responses/expectancies about environmental cues</td>
</tr>
<tr>
<td>INTENTION/COMMITMENT/PLANNING</td>
<td>Intending or planning to perform the behavior; setting goals or making a commitment to perform the behavior</td>
<td>One has formed strong behavioral intentions to engage in the behavior; one has set realistic goals or made a firm commitment to engage in the behavior</td>
<td>Behavioral intentions</td>
<td>Behavioral intentions</td>
<td>Self-control/self-regulation</td>
<td>Contemplation/preparation (stages of change); self-liberation (process of change)</td>
</tr>
</tbody>
</table>

below that range contains 16% of the values. A range encompassing \( \pm 2 \) SD includes 95% of the values (with the upper and lower tails each comprising approximately 2.5% of the values), and \( \pm 3 \) SD encompasses 99.7% of the values (Table 6-4 and Fig. 6-5).

For any single measurement, its distance away from the mean can be expressed in terms of the number of SDs (also called a \( z \) score); one can then consult a table of the normal distribution to find out what percentage of measurements fall within that distance from the mean. Software to convert anthropometric data into \( z \) scores for epidemiologic purposes is available. A measurement that falls “outside the normal range”—arbitrarily defined as 2, or sometimes 3, SDs on either side of the mean—is atypical, but not necessarily indicative of illness. The further a measurement (say, height, weight, or IQ) falls from the mean, the greater the probability that it represents not simply normal variation, but rather a different, potentially pathologic, condition.

Another way of relating an individual to a group uses percentiles. The **percentile** is the percentage of individuals in the group who have achieved a certain measured quantity (e.g., a height of 95 cm) or a developmental milestone (e.g., walking independently). For anthropometric data, the percentile cutoffs can be calculated from the mean and SD. The 5th, 10th, and 25th percentiles correspond to \( -1.65 \) SD, \( -1.3 \) SD, and \( -0.7 \) SD, respectively. Figure 6-4 demonstrates how frequency distributions of a particular parameter (height) at different ages relate to the percentile lines on the growth curve.

**Bibliography is available at Expert Consult.**
Bibliography
From Freud to Skinner to Piaget, philosophers, psychologists, and psychiatrists used to think that babies and young children were solipsistic and egocentric, precausal and illogical, concrete and superficial, restricted to the immediate here and now. That is still the picture most parents and many pediatricians have of babies and young children.

But 3 decades of research shows that just the opposite is true. Even the youngest babies both know more and learn more than we would ever have thought. There are still many controversies about exactly what babies and children know and when they know it. There also are competing theories about how and why children know and learn so much.

**METHODOLOGIES**

Much of this new understanding is the result of new techniques. Psychoanalysts asked adults to remember their childhood, behaviorists extrapolated from experiments on animals, and even Jean Piaget, the founder of the field of cognitive development, relied on observing the spontaneous behavior of babies, or on clinical interviews in which he asked children to say what they thought about mind and body or life and death. We now have experimental techniques that let children tell us what they know in their own language.

One group of methods involves seeing what babies prefer to look at (visual preferences), or listen to, or even smell. Babies have a choice of two stimuli, such as a mother's voice playing in one speaker, while a stranger's plays in another. We can see if babies turn toward one stimuli or the other.

Other methods use the fact that babies pay more attention to things that are unexpected than to those that are more predictable or familiar. Babies are *habituated* to a stimulus; they look or listen until their attention wanders, and when they see a variant of that stimulus they focus attention to the new stimulus if it is different. In violation-of-expectation studies, experimenters present babies with events that are surprising from an adult point of view, for example, one object apparently moving through another, and see whether babies look longer at those events than at similar unsurprising events.

These *looking-time* techniques have a drawback: it is difficult to tell just how babies interpret the stimulus by simply recording whether they look at it. Other technologies have made it possible to actually track babies' eye movements as they look at a stimulus. We can also look at what babies do as well as at what they attend to. Watching where babies reach or what they point to can be highly informative. Babies begin to imitate other people literally from birth and seeing how that imitation unfolds has proved to be a particularly useful tool.

As children grow older their attention patterns become less predictable. On the other hand, we can listen to what toddlers and preschoolers say. Large databases that record and analyze children's spontaneous language are becoming increasingly sophisticated, and can be an invaluable source of insight.

Asking preschoolers what they think often produces a sort of stream-of-consciousness poem, and has undoubtedly contributed to the impression that preschoolers are irrational. Children behave much more intelligently when you ask them about restricted, highly detailed scenarios. Instead of asking “Can someone believe something that isn’t true?” researchers tell children a specific story—Max sees some
chocolate in the yellow cupboard, but then it is transferred to the blue cupboard without his knowledge. Preschoolers are even likely to respond to open-ended questions with silence or irrelevance. But they will consistently pick one option over the other when you ask them to choose between them. Four-year-olds can say that Max will look for the chocolate in the blue cupboard rather than the yellow one.

**PHYSICAL KNOWLEDGE DEVELOPMENT**

From the time infants are very young they understand some of the basic properties of physical objects. In the first few months of life, they know that objects are 3-dimensional and extended in space, that they can’t pass through other objects, and that they continue to exist when they move behind a screen. They also have a basic concept of numbers, at least up to 3. In one experiment, infants see a toy disappear behind a screen, and then see another toy move behind the screen. The screen is lifted and 1, 2, or 3 toys appear. The babies look longer if 1 or 3, rather than 2, toys appear.

Infants also have a surprisingly early understanding of relationships that cross sensory modalities. They recognize parallelisms between lip movements and vocal sounds, between the feel of a pacifier and the way it looks, or between the visual image of a bouncing ball and the sound it makes.

Babies also have a surprisingly early and sophisticated understanding of statistics and probability. Before they are 1 yr old, they expect that a ball taken at random from a box of 80 red and 20 white balls is more likely to be red than white. Infants can also recognize statistical patterns in both visual and auditory sequences. You can play babies a string of syllables or tones or show them a sequence of pictures that have a particular pattern. For example “pa” may always follow “ti” but only follow “ko” 75% of the time. Babies seem to figure out these statistical patterns. Later they use them to isolate words or objects or other meaningful units from the torrent of sounds and sights they perceive.

In their second year, babies have a basic understanding of spatial relationships like gravity and containment. They can also categorize objects, recognizing that animals, for example, go together and are different from artifacts. They also gradually come to understand how to use simple tools to accomplish what they want, although they may still make interesting mistakes, like pulling a blanket to try to get a toy even when the toy is beside the blanket instead of on top of it.

Preschoolers continue to learn about the physical world, but they also begin to learn about the biologic world. Three and 4 yr olds are essentialists. They assume that categories of animals or plants, such as birds or daisies, will have the same insides and the same essence even if they are perceptually diverse. Contrary to conventional wisdom, preschoolers are not restricted to superficial perceptual categories. Preschoolers also have a first understanding of basic biologic ideas like inheritance, growth, and illness, and don’t confuse these with psychologic ideas; they are not animists as Piaget thought. However, they still have difficulty understanding biologic concepts in a unified way, and they have little understanding of death.

By 5 yr of age, preschoolers have a more unified concept of something like a life force. They believe that the presence of this force makes living things grow and thrive, and its absence leads to illness and death. Interestingly, disadvantaged rural children, for example, Native American children on Indian reservations, who may have more experience of the living world, may develop an understanding of biology earlier than more privileged middle-class children.

Preschoolers also have a much more sophisticated understanding of causal relationships than we previously thought. Infants even understand something about the way physical objects move and interact with other objects. Older children understand the mechanics of simple physical systems.

They can also learn about new causal relationships. We can give young children evidence about how a novel machine works, showing them for instance that a box lights up and plays music only when you put a specific combinations of blocks on it. Children as young as 2 yr of age can figure out how the machine works and can use that information to invent novel ways to make it go. By 4 yr, they can figure out a machine that involves complex interactions of 3 different gears and switches. They can even propose invisible unobserved causes, when that is the best explanation for the pattern of evidence. In fact, they use forms of inductive causal reasoning that are basic to science and that are used in computer learning.

**SOCIAL KNOWLEDGE DEVELOPMENT**

Some of the most impressive kinds of early knowledge and learning involve children’s understanding of other people. These theory-of-mind abilities are particularly important for social interaction and appear to be specifically impaired in children with autism. From the time they are born, infants treat people as special. Within the 1st mo infants prefer to look at human faces and listen to human voices, and rapidly prefer the face, voice, and even smell of their caregivers. Newborn infants also imitate facial expressions. To do this they must link what they see on the face of another person and how it feels to be them inside.

Within the 1st yr babies develop an even richer understanding of others. Seven-month-olds appreciate that human actions are directed towards particular goals. You can show the babies a ball and a teddy bear on a table. A hand reaches in and grasps the ball. Now you switch the locations of the 2 toys, so that the teddy bear is where the ball was and vice-versa. Seven-month-olds look longer when the hand goes to the teddy bear instead of the ball. They don’t do this if a stick, rather than a hand, touches one object or the other.

One-year-olds don’t just imitate actions; they reproduce the results of those actions. A 1 yr old child walks into the lab and sees the experimenter tap his head on a box, making the box light up. A week later she returns to the lab and sees the box on the table. She’ll immediately use her own head to get the box to light.

Eighteen-month-olds can imitate in an even more sophisticated way. You can show them an experimenter touching her head to the box, but now she has a blanket wrapped around her so that her hands aren’t available. If the other person’s hands are free the babies will tap their own heads on the machine. But if she’s wrapped up in the blanket and she taps the machine with her head, the babies will instead use their own hands. They’ve figured out that you would use your hands if you could, but because you can’t, you’re using your head instead.

In their second year, children also start to understand that their own perceptions, attention, and emotion may be shared by others. At this age babies start to engage in joint attention behaviors; they will follow the gaze or point of another person and they will point to objects themselves. They also start to understand that closing your eyes or wearing a blindfold may make it more difficult to see. In social referencing, babies will react appropriately to the emotional expression of another person that is directed at an object; if 1 yr olds see someone react to an ambiguous object with fear they will avoid the object themselves.

Babies are also sensitive to the contingency between their own actions and the actions of others, and use contingency patterns to differentiate people and things. If 1 yr olds see a machine that blinks and chirps in coordination with their own actions, they will treat it like a person, following its gaze if it turns toward an object. They will not do this if the machine makes the same noises, but they are not contingent on the baby’s actions.

Eighteen-month-olds also start to show an understanding of love. Attachment researchers have long noted that different babies behave differently when they are separated from their caregivers and then reunited. Secure babies are distressed at separation but are quickly comforted when the caregiver returns. Avoidant babies seem to repress their distress; they ignore the caregiver both when she leaves and returns. Anxious babies are very distressed and take a long time to comfort.

Secure and insecure babies seem to have different theories of love. In one experiment, 18 mo old babies saw an animated film of a mother figure, a big circle, and a baby figure, which was a small circle that emitted a realistic cry. Then the babies either saw that the mother moved towards the baby or moved away from the baby. The secure babies expected that the mother would return to the baby and looked longer when she did not. The insecure babies had just the opposite theory; they looked longer when the mother changed course and returned.
From 2-6 yr of age, children discover further fundamental facts about how their own minds and the minds of others work. Even 18 mo olds already seem to understand something about the ways that people's minds might differ. You can show 14 mo olds and 18 mo olds 2 bowls of food: raw broccoli and Goldfish crackers. Then the experimenter tastes a bit of food from each bowl and acts as if she likes the broccoli but not the crackers. She puts out her hand and says, "Can you give me some." Fourteen-month-olds give the experimenter the crackers, but the 18 mo olds give the experimenter broccoli.

Slightly older children can understand the complex causal interactions between desire, perception, and emotion; they can predict all the possible actions that might stem from different psychologic combinations.

Preschoolers also, against conventional wisdom, can understand the difference between the physical and the mental, reality and fantasy, from a very young age. Preschoolers may be intensely emotionally affected by the products of fantasy, from imaginary friends to monsters in the closet. Nevertheless, they recognize the distinction between imaginations, which are private and intangible, and reality, which is public and verifiable.

In addition, around 5 yr of age children start to understand the relationship between our beliefs and the world around us. For example, suppose you show a child a candy box that turns out to be full of pencils. The children are very surprised when they see the pencils. But if you ask them what they thought was in the box 3 yr olds confidently report that they thought there were pencils in there. You see the same thing in the "Max" experiment described earlier. Though 4 yr olds accurately report where Max will look for the chocolate, 3 yr olds say that Max will look for the chocolate where it actually is instead of where he thinks it is.

Similarly, 3 yr olds have difficulty understanding the sources of their beliefs. If you ask them how they learned something, they are likely to think that they saw it directly, even when they actually heard it from someone else—an important consideration in child testimony. In their spontaneous language children only start explaining actions in terms of thoughts and beliefs, especially false thoughts and beliefs, when they are around 4 yr old. There are somewhat controversial studies that suggest that some implicit and unconscious understanding of belief may even be in place earlier, but there are clearly important changes in children's conscious understanding of the mind between 3 and 5 yr of age.

Understanding the mind also allows children to act to change the minds of others. Children who can explain actions in terms of a theory of mind also seem to be more adept, for good or ill, at altering other people's minds. They are more socially skillful, but they are also better liars.

Understanding minds actually also allows us to change our own minds as well as the minds of others. Between 3 and 5 yr of age, children also start to develop capacities for what psychologists call executive control, which is the ability to control your own actions, thoughts, and feelings. These capacities seem to be specifically related to theory-of-mind abilities. Understanding how your own mind works may help you to control and regulate it.

THEORIES OF COGNITIVE DEVELOPMENT

Several alternative theories have been proposed to explain these developmental processes. The basic conundrum of cognitive development is that even the youngest babies seem to have abstract, highly structured, hierarchical knowledge of the world; knowledge that lets them make wide-ranging new inferences. And yet as children experience more of the world, these representations change in systematic ways; it appears that young children are learning from their experiences.

One classic approach, often called nativism suggests that much of this abstract structure is in place innately; babies are born knowing about crucial aspects of the world. Learning is largely just a matter of filling in details. Although babies are far from being blank slates, there also seem to be significant changes in their understanding of the world.

The alternative approach, empiricism, suggests that all of children's knowledge is simply the result of a process of associating or combining particular sensory experiences, or detecting the statistics of the environment. Although children are able to associate particular experiences and to detect statistics, those abilities don't seem to be sufficient to explain their remarkable growth of knowledge.

Piaget originally articulated constructivism as an alternative to both nativism and empiricism. But Piaget had little to say in detail about how constructivist processes could take place; many of his empirical claims have been disproved. The theory of theory is the more current version of constructivism. The idea is that children develop their knowledge of the world by constructing every day or intuitive theories, much like scientific theories. The theory theory, unlike empiricism, proposes that even babies may be born with innate theories of the world, but unlike nativism, it proposes that those theories may be radically transformed as children learn more about the world. Most recently, rational constructivism, a more rigorous and precise version of the theory theory, was formulated. It uses mathematical ideas about probabilistic models and bayesian inference to explain how even very young children can learn so much from the evidence they encounter.

Within the constructivist approach, an exciting new set of studies and theoretical ideas confirms something that parents and preschool teachers and others have long thought intuitively: Very young children's play, both their exploratory play and their imaginative and pretend play, contributes greatly to their early learning.

Nativism, empiricism, and constructivism all focus on the process of learning from evidence. Two other approaches describe other factors that contribute to cognitive development. Information-processing approaches stress the development of general abilities to process and organize information, such as memory or attention. Indeed, children do develop such abilities in the first few years of life and those developments contribute to the development of their knowledge.

Sociocultural approaches emphasize the contribution that expert adults can make to children's knowledge. There is growing evidence that from very early in infancy babies are specifically and powerfully tuned to information that comes to them from their caregivers. By preschool, what is sometimes called implicit or intuitive pedagogy plays an increasingly important role in children's learning. Preschoolers tend to give grownup testimony the benefit of the doubt, but they can also distinguish between reliable and unreliable teachers.

However, preschoolers sensitivity to implicit teaching can be a double-edged sword. Some studies show that children are less likely to engage in wide-ranging exploration when adults provide them with answers. Preschoolers left to their own resources are often able to solve complex problems (see Chapter 7.1). In addition because play is such an important component of a preschool-age child's learning process, the learning environment may need to be less structured, more child-focused, and with less emphasis on traditional academic instruction. Sociocultural approaches are especially relevant to the many kinds of learning where there is no right answer such as learning the particular traditions, mythologies, or values of your cultural or ethnic group.

All these factors, innate structure, association and statistics, theory formation and play, information-processing abilities, and cultural transmission, must somehow combine to allow children to learn as much as they do.

Bibliography is available at Expert Consult.

7.1 The Reggio Emilia Educational Approach and Child Development and Learning

Naama Zoran and Rivkie Spalter

Maria Montessori was the first to bring the message of children as competent, and was followed by Loris Malaguzzi who had the same philosophy and developed his approach in Reggio Emilia, a city in Italy. Malaguzzi believed that education is a lifetime experience that has 3
Bibliography
major elements: the emotional component, the ethical component, and the aesthetic component.

**THE EMOTIONAL COMPONENT**
Malaguzzi believed that the concept of well-being leads the educational approach. Well-being, especially in early childhood, is the leading developmental task that every child from birth is thriving for as part of each child’s sense of self-establishment. Creating an educational environment that recognizes the child’s social–emotional well-being means creating a place where every child is valued and respected as an individual and as an equal member of a group. Malaguzzi believed that every moment should be enjoyable and satisfactory (Box 7-1).

**THE ETHICAL COMPONENT**
The following points characterize the Reggio Emilia ethical code:

- Education is not just a technique but is a shared process for revealing values.
- The school is a place that transmits and constructs culture through experiences. The reciprocal relations between transmission and construction gives schools and teachers a responsibility and an active role in sustaining and generating a culture that is based on the past, yet looking ahead to the future.
- The school should focus not only on knowledge but also on concepts, ideas, and values.
- The educator influences the future, and as such needs to generate the connections between the individual and the world.
- Children are born with myriad ways to construct and process knowledge. Those ways are defined as 100 languages; language is defined as the different ways through which any human being represents, communicates, and expresses thoughts, feelings, concepts, and symbols (Box 7-2).

**THE AESTHETIC COMPONENT**
Education must focus on the aesthetics because the child knows how to value beauty and is able to interact with all the expressive languages. Malaguzzi’s innovative idea for approaching and embracing the expressive–aesthetic aspects to early childhood education was the atelier. The atelier is a statement about the importance of imagination, creativity, expression, and aesthetics in the learning and knowledge construction processes. Because children do not separate different disciplinary fields, and because they learn in an interconnected and interdisciplinary way, the learning environment should connect between aesthetics and ways of knowing. The expressive languages and the arts are ways to break the conformist thinking about children and their learning, and to move toward elaborating the opportunities that are given to children while they are exploring, researching, and constructing knowledge.

**PEDAGOGIC THINKING: CORE CONCEPTS AROUND 3 MAJOR AREAS**
One of the cornerstones of this approach is the concept of images (Fig. 7-1).

An image is a cognitive structure that serves as a container. It keeps and holds all of the tools we have to perceive and interpret the world around us. All of the perceptions and interpretations are organized into clusters that serve as our inner compass and navigate our way in the personal and social–cultural life that we share with others.

When it comes to education, the images play a crucial and determinant role as is reflected in the following quote from Carla Rinaldi: “Everyone (you, us, each parent…) has his or her own image of the child, and, consequently, we have our own educational theories that we develop based on personal, social, cultural, and political experience, and that we construct or acquire as part of our society and culture. Whether we are aware of it or not, we cannot live without theories.” Yet, as educators we have a profound responsibility for the awareness level that guides us when we make choices for children.

It is important to note that each person has his or her own image of the child. By saying image we mean personal interpretation that is subjective and unique. The focus is on which point of view being used when thinking about a child. Our points of view about the world around us are dynamic and are consistently changing. We are structuring the impressions we are getting on any concept or experience to create a holistic image in our mind.

**The Image of the Child**
Loris Malaguzzi said “Each has inside ourselves an image of the child that directs you as you begin to relate to a child. This theory within you pushes you to behave in certain ways.” It orients you when you listen to the child, observe the child. It is very difficult for you to act contrary to this internal image.

It is important to emphasize the impact of the image to the awareness of the teachers, as only the awareness would enable the teacher to follow the desired image of children; one that sees and accepts the
child as an active competent partner, plentiful with potential and capabilities. Usually the strength and the talents of children are underestimated and schools tend to suppress the child’s potential by creating an environment of transmission, instead of exploration. The environment should be collaborative between teachers and children; they partner together rather than the teacher determining all activities or interactions.

The concept of a “blank slate,” first mentioned by the philosopher John Locke, is presented here as a characterizing traditional point of view in education that does not believe in the child’s abilities and leaves no room for the child’s feelings, thoughts, imagination, and creativity. It also reflects the belief that the child is waiting for the school and society to “write” on, nourish, and fill his or her slate.

Choosing an image calls for a sense of responsibility, as we need to commit to the image that was chosen. The chosen image then becomes a compass that guides us in every interaction or practice we are having with the child. Reggio educators believe that the image of child as competent brings a point of view that sees children as structuring their sense of self, they generate and construct values, and they establish their rights; the first one is the right that acknowledges and accepts the role childhood has and the unique contribution each person brings to it.

The child is born as a researcher that is looking for relationships, hypotheses, and provocations in anything the child is exploring. The choice to see the child as a researcher has major pedagogical implications. The first guiding implication is the understanding that the child is never waiting for the adult to actuate the child’s need to research, yet the child needs the adult as a context for the child’s revelations (Box 7-3).

The Image of the Educator

The core component in the image of the teacher is the understanding that to be a high-quality teacher, the educator needs to perceive himself or herself also as a learner. The most meaningful place for learning how to teach is within the educational setting. You learn how to teach by being with children and by reflecting on the processes you have experienced with them; the best key for learning and teaching is reciprocity.

The role of the teacher in the above image encompasses the following aspects:

- To define and create the context within which all learning/teaching processes would occur. The context enables the landscape of learning to emerge and develop.
- To think and plan using symbols and concepts
- To interpret the child concepts and symbols with the group
- To elaborate on the experiences and the interpretations done with the children.
- To review with the children a second round of experiences built on the previous day.
- To add improvisations according to the previous learning processes.

There are reciprocal relationships between the image of the child and the image of the teacher, and each is complementary and bound to the other.

Teachers should never think of the child in the abstract. When we think about a child, that child is already tightly connected and linked to a certain reality. Children have relationships and experiences that they bring to any new environment. Similarly, the teacher brings pieces of his or her life to the educational environment (Box 7-4).

The Image of the Contextual Community

The concept at the core of the educational communal life is the idea of the “other” that is the essence of the Reggio Emilia pedagogic approach. The “other” might be the child, the family, or a colleague—in a sense, any person who is interacting with the educational system. All members together, through the relations that are constructed among all, are part of creating a sense of belonging for the system and for its members. The feeling of belonging serves as a foundation for the community life. When people who are part of the system feel they are seen, heard, and known, a culture of participation can be developed. The culture of participation arises out of the integration of the concept of feeling a part of, and its complementary aspect of taking part, and is shared among all children, parents, and teachers.

The focus was and is to develop relationships with the other, with the other’s uniqueness and originality, with the other’s point of view, and to reach the place where the subjectivity of each partner is open to entering an intersubjective field for a real meeting. The basic assumption is that each family shares its culture with the others.

The idea of crossing the boundaries of the subjectivity to arrive at the intersubjective landscape emerges from a very important declaration that the school sends to the community: A declaration of a place that has a defined and solid identity that is based on the perception that the school by nature is a multicultural place, and as such embraces every inhabitant, including each inhabitant’s background and culture, knowing that the school point of view is partial, and each is invited to share their points of view, as the school invites each partner to add their point of view for strengthening, elaborating, and accommodating the shared identity of the school.

Concepts like welcoming, plurality, dialog, and intercultural dynamics are explored and new meanings are attributed to them, as a realization that every word/concept or value could have different meanings. That realization creates a place for reworking of the ideas, a place where new questions are generated and discussed.

THE DEVELOPMENTAL THEORIES OF GREENSPAN, VYGOTSKY, AND MALAGUZZI

Greenspan on Well-Being and the Sense of Self

Stanley Greenspan (1941–2010), a psychiatrist, was a leading researcher on the prevention and treatment of emotional and developmental disorders in infants and children. He believed that when you observe or interact with a child, you should take into account not just the child’s developmental functioning level, but also the child’s background, personal and familial history, and, especially, the quality of relationships the child is experiencing in his or her home and school environment.

Greenspan believed that it is the quality of the interactions children have with meaningful figures that determines the quality of the social–emotional experiences and the level of success in achieving the developmental tasks that are required in every developmental sequence. Greenspan developed a model that shows how in every developmental phase, 2 different processes are possible. Simply stated, high-quality responsive parenting leads to high-quality achievement of the
Comparison of Greenspan and Malaguzzi Developmental Theories

<table>
<thead>
<tr>
<th>DEVELOPMENTAL PRINCIPLE</th>
<th>GREENSPAN</th>
<th>MALAGUZZI (REGGIO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-regulation</td>
<td>The ability to reach an inner and outer harmony. The harmony represents the skills needed to create the initial understanding of being in the world.</td>
<td>The school environment is designed and organized in ways that support the concept of being in harmony. In Malaguzzi’s words, an “amiable environment.”</td>
</tr>
<tr>
<td>Attachment and bonding</td>
<td>The ability to create a meaningful, special bond with another; plant the seeds for the notion of love and be loved.</td>
<td>Well-being is the fountain for all the relationships, and the school is the landscape of well-being that is ready to embrace all kinds of relationships.</td>
</tr>
<tr>
<td>Differentiation</td>
<td>The ability to differentiate oneself from any other person is crucial for the sense of separation and uniqueness.</td>
<td>The child is seen as a unique individual, who is at all times an active and equal member of the school community.</td>
</tr>
<tr>
<td>Initiation and internalization</td>
<td>The ability to navigate oneself in the world in an active, participatory way, that empowers and leads to the internalization of the sense of self.</td>
<td>One of the core concepts that defines curricular planning and guides teachers’ practical choices is the ability of the school to define the educational intents in visible and declarative ways that support the curricular initiatives and their impact on the school community.</td>
</tr>
<tr>
<td>Representational thinking</td>
<td>The ability to represent all of the above in a verbal, conceptual, socially and emotionally appropriate way.</td>
<td>The concept of the “hundred languages of children” is a message that there are a hundred ways to represent the knowledge and understanding that was achieved in any learning experience.</td>
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Vygotsky and the Reggio Emilia Approach

Vygotsky’s concept of the zone of proximal development states that in any given moment, the person (child or adult) finds himself between 2 developmental points—the actual and the potential points of development that represent the idea of human competence. Vygotsky saw the actual point of development as the place that reflects the already existing skills in all areas of development, and the potential point of development as the place for the skills on which the person works at that given time. Between those 2 points of development is the land of development, where each of us is using what we already have in order to develop what is potentially waiting to unfold.

Vygotsky believed that the teacher’s role is to be with children in a very conscious and attentive way. To use the child’s actual point of development as the launching place for challenges that would encourage further exploration and learning.

Malaguzzi believed that being with children in their developmental journey calls for deep engagement and attentiveness by the teacher in order to meet all children individually and in small groups in terms of where they are in their interests, exploration, and research. The main goal is to create the most meaningful learning environment that supports the actualization of their potential. According to Malaguzzi, the level of engagement of the teachers is not narrowed only to their actions but includes investment in observations, interpretations, and reflections that are the grounds for the practical actions.

Vygotsky’s social construct is known for its relevance to the educational field. One of Vygotsky’s leading concepts is the scaffolding process that defines a specific interaction between teachers and learners in which the teacher supports the learning process in situations where the learner cannot explore or research alone. Connected to the scaffolding concept is the question of the relations between scaffolding and giving help when it comes to relationships with children. Vygotsky’s scaffolding concept highlights the difference between authentic and nonauthentic support of children’s learning processes and focuses on giving only the support that would enable the child to move toward the child’s potential point of development, according to the child’s developmental pace. This was interpreted by Malaguzzi as things that children can do by themselves should not be done for them. It is only when the child needs the bridge between the child’s current place and the child’s destination that adults should step in delicately and consciously and provide help (Box 7-5).

Box 7-5 Example of Giving Only the Support That Enables a Child to Move Toward the Child’s Potential Point of Development, According to the Child’s Developmental Pace

The children were playing with a large box that was brought to the school. One of the kids climbed in and suddenly realized he was stuck and could not climb out. The child began to cry. The teacher asked him what he could do to solve the problem, and his response was: “I will ask my friends.” He called his friends and they began giving him ideas.

One child tried to pull him out, but the box was too tall. Two other friends came, brought a chair, and tried to pull him out, but still the box was too tall.

Then a fourth child joined and suggested putting a chair INSIDE the box. The children brought a chair that was put inside, and their friend climbed out happy and empowered.

Reggio Approach and Relationships with Parents

In the Reggio approach, the image of the parent parallels the image of the child. In other words, as the child is seen as an equal, active, and competent partner, the parent is also perceived as a competent, active partner to the educational endeavor. The core of the relationship is the value of parent participation with 2 cornerstones. First is the idea of taking part in the different ways parents can participate in school life. Second is the emotional attitude parents establish toward the school. The integration of those 2 cornerstones creates a way of being in the schools that represents a democratic approach to citizenship with solidarity and shared responsibility as core guidelines.

The ethical code for the participatory approach is that each member in the educational process brings his or her forms of knowing, points of view, interpretations of different experiences, and culture. The participation sets the ground to discussions and rich exchanges among the parents and the school that open the door for wide-ranging discussions.
The uniqueness of the participatory way of being in the Reggio Emilia approach is the belief that only by accepting other persons from a humanistic point of view, can real acceptance and acknowledgement arise. The parent usually has his or her own image of the child that is based on the relationships, culture, and family traditions, history, and characteristics. The deep relationship with the school enables the parent to gain a different image of his or her child. The opportunity to widen the personal image and to integrate the personal image with the school image opens a door for a wider and deeper relationship between parents and their children.

Bibliography is available at Expert Consult.
Bibliography
Chapter 8
Assessment of Fetal Growth and Development

Susan Feigelman

The developing fetus is affected by social and environmental influences, including maternal nutritional status; substance use (both legal and illicit); and psychologic trauma. Correspondingly, the psychologic alterations experienced by the parents during the gestation profoundly impact the lives of all members of the family. Growing evidence implicates the importance of these and other maternal and paternal experiences that occur during and prior to the pregnancy (and even among members of earlier generations) on the subsequent development of the individual (epigenetic effects). The complex interplay between these forces and the somatic and neurologic transformations occurring in the fetus influence growth and behavior at birth, through infancy, and potentially throughout the individual's life.

SOMATIC DEVELOPMENT

Embryonic Period

Table 8-1 lists milestones of prenatal development. By 6 days postconception age, as implantation begins, the embryo consists of a spherical mass of cells with a central cavity (the blastocyst). By 2 wk, implantation is complete and the uteroplacental circulation has begun; the embryo has 2 distinct layers, endoderm and ectoderm, and the amnion has begun to form. By 3 wk, the 3rd primary germ layer (mesoderm) has appeared, along with a primitive neural tube and blood vessels. Paired heart tubes have begun to pump.

During wk 4-8, lateral folding of the embryologic plate, followed by growth at the cranial and caudal ends and the budding of arms and legs, produces a human-like shape. Precursors of skeletal muscle and vertebrae (somites) appear, along with the branchial arches that will form the mandible, maxilla, palate, external ear, and other head and neck structures. Lens placodes appear, marking the site of future eyes; the brain grows rapidly. By the end of wk 8, as the embryonic period closes, the rudiments of all major organ systems have developed; the crown-rump length is 3 cm.

Fetal Period

From the 9th wk on (fetal period), somatic changes consist of rapid body growth as well as differentiation of tissues, organs, and organ systems. Figure 8-1 depicts changes in body proportion. By wk 10, the face is recognizably human. The midgut returns to the abdomen from the umbilical cord, rotating counterclockwise to bring the stomach, small intestine, and large intestine into their normal positions. By wk 12, the gender of the external genitals becomes clearly distinguishable. Lung development proceeds, with the budding of bronchi, bronchioles, and successively smaller divisions. By wk 20-24, primitive alveoli have formed and surfactant production has begun; before that time, the absence of alveoli renders the lungs useless as organs of gas exchange.

During the 3rd trimester, weight triples and length doubles as body stores of protein, fat, iron, and calcium increase.

NEUROLOGIC DEVELOPMENT

During the 3rd wk, a neural plate appears on the ectodermal surface of the trilaminar embryo. Infolding produces a neural tube that will become the central nervous system and a neural crest that will become the peripheral nervous system. Neuroectodermal cells differentiate into neurons, astrocytes, oligodendrocytes, and ependymal cells, whereas microglial cells are derived from mesoderm. By the 5th wk, the 3 main subdivisions of forebrain, midbrain, and hindbrain are evident. The dorsal and ventral horns of the spinal cord have begun to form, along with the peripheral motor and sensory nerves. Myelination begins at midgestation and continues for years.

By the end of the embryonic period (wk 8), the gross structure of the nervous system has been established. On a cellular level, neurons migrate outward to form the 6 cortical layers. Migration is complete by the 6th mo, but differentiation continues. Axons and dendrites form synaptic connections at a rapid pace, making the central nervous system vulnerable to teratogenic or hypoxic influences throughout gestation. Figure 8-2 shows rates of increase in DNA (a marker of cell number), overall brain weight, and cholesterol (a marker of myelination). The prenatal and postnatal peaks of DNA probably represent rapid growth of neurons and glia, respectively. By the time of birth, the structure of the brain is complete. Synapses will be pruned back substantially and new connections will be made, largely as a result of experience. Many psychiatric and developmental disorders are thought to result at least in part from disruptions in the functional connectivity of brain networks. Disorders of connectivity may begin during fetal life; MRI studies provide a developmental timetable for such connections that lend support to the possible role of disruptions in the establishment of such connections during fetal life.

BEHAVIORAL DEVELOPMENT

No behavioral evidence of neural function is detectable until the 3rd mo. Reflexive responses to tactile stimulation develop in a craniocaudal sequence. By wk 13-14, breathing and swallowing motions appear. The grasp reflex appears at 17 wk and is well developed by 27 wk. Eye
basic form of learning in which repeated stimulation results in a response decrement. If the tone changes in pitch, the movement increases again, which is evidence that the fetus distinguishes between a familiar, repeated tone and a novel tone. Habituation improves in older fetuses, and decreases in neurologically impaired or physically stressed fetuses. Similar responses to visual and tactile stimuli have been observed.

**PSYCHOLOGIC CHANGES IN PARENTS**

Many psychologic changes occur during pregnancy. An unplanned pregnancy may be met with anger, denial, or depression. Ambivalent feelings are the norm, whether or not the pregnancy was planned. Elation at the thought of producing a baby and the wish to be the perfect parent compete with fears of inadequacy and of the lifestyle changes that mothering will impose. Parents of an existing child feel protective for the existing child, worried that the existing child may feel less valued. Old conflicts may resurface as a woman psychologically identifies with her own mother and with herself as a child. The father-to-be faces similar mixed feelings, and problems in the parental relationship may intensify.

Tangible evidence that a fetus exists as a separate being, whether as a result of ultrasonic visualization or awareness of fetal movements (at approximately 20 wk), often heightens a woman's feelings. Parents worry about the fetus's healthy development and mentally rehearse what they will do if the child is malformed, including their response to evidence of abnormality through ultrasound, amniocentesis or other fetal laboratory tests. Toward the end of pregnancy, a woman becomes aware of patterns of fetal activity and reactivity and begins to ascribe to her fetus an individual personality and an ability to survive independently. Appreciation of the psychologic vulnerability of the expectant parents and of the powerful contribution of fetal behavior facilitates supportive clinical intervention.

**THREATS TO FETAL DEVELOPMENT**

Mortality and morbidity are highest during the prenatal period (see Chapter 93). An estimated 50% of all pregnancies end in spontaneous abortion, including 10-20% of all clinically recognized pregnancies. The vast majority occur in the 1st trimester. Some occur as a result of chromosomal or other abnormalities.
Teratogens associated with gross physical and mental abnormalities include various infectious agents (toxoplasmosis, rubella, syphilis); chemical agents (mercury, thalidomide, antiepileptic medications, and ethanol), high temperature, and radiation (see Chapters 96 and 718).

Teratogenic effects may also result in decreased growth and cognitive or behavioral deficits that only become apparent later in life. Nicotine has vasoconstrictor properties and may disrupt dopaminergic and serotonergic pathways. Prenatal exposure to cigarette smoke is associated with lower birthweight, shorter length, and smaller head circumference, as well as changes in neonatal neurodevelopmental assessments. Later, these children are at increased risk for learning problems, externalizing behavior disorders, and long-term health effects. The effects of prenatal exposure to cocaine, also occurring through alternations in placental blood flow and in direct toxic effects to the developing brain, have been followed in several cohorts and are less dramatic than previously believed. Exposed adolescents show small but significant effects in behavior and functioning, but may not show cognitive impairment. The associated risk factors including other prenatal exposures (alcohol and cigarette co-use) as well as “toxic” postnatal environments frequently characterized by instability, multiple caregivers, and violence exposure remain significant (see Chapters 39 and 40).

The association between an inadequate nutrient supply to the fetus and low birthweight has been recognized for decades; this adaptation on the part of the fetus presumably increases the likelihood that the fetus will survive until birth. For any potential fetal insult, the extent and nature of its effects are determined by characteristics of the host as well as the dose and timing of the exposure. Inherited differences in the metabolism of ethanol, timing of exposure, and the mother’s diet may explain the variability in fetal alcohol effects. Organ systems are most vulnerable during periods of maximum growth and differentiation, generally during the 1st trimester (organogenesis). http://www2.epa.gov/children/children-are-not-little-adults details critical periods and specific developmental abnormalities.

Fetal adaptations or responses to an adverse situation in utero (referred to as fetal programming or developmental plasticity) have lifelong implications for the individual. Fetal programming may prepare the fetus for an environment that matches that experienced in utero. Fetal programming in response to some environmental and nutritional signals in utero increase the risk of cardiovascular disease, diabetes, and obesity in later life. These adverse long-term effects appear to represent a mismatch between fetal and neonatal environmental conditions and the conditions that the individual will confront later in life; a fetus deprived of adequate calories may or may not as a child or teenager face famine. One proposed mechanism for fetal programming is epigenetic imprinting, in which two genes are inherited but one is turned off through environmentally induced epigenetic modification (see Chapters 80 and 81.1). Imprinted genes play a critical role in fetal growth and thus may be responsible for the subsequent lifelong effects on growth and related disorders.

Just as the fetal adaptations to the in utero environment may increase the likelihood of later metabolic conditions, the fetus adapts to the mother’s psychologic distress. In response to the stressful environment, physiologic changes involving the hypothalamic–pituitary–adrenal axis and the autonomic nervous system occur. Dysregulation of the hypothalamic–pituitary–adrenal axis and autonomic nervous system may explain the associations observed in some but not all studies between maternal distress and negative infant outcomes, including low birthweight, spontaneous abortion, prematurity, and decreased head circumference. In addition, children born to mothers experiencing high stress levels have been found to have higher rates of inattention, impulsivity, conduct disorders, and cognitive changes. Although these changes may have been adaptive in primitive cultures, they are maladaptive in modern societies, leading to psychopathology. Genetic variability, timing of stress during sensitive periods, and the quality of postnatal parenting can attenuate or exacerbate these associations.

Bibliography is available at Expert Consult.
Bibliography
Regardless of gestational age, the newborn (neonatal) period begins at birth and includes the 1st mo of life. During this time, marked physiologic transitions occur in all organ systems, and the infant learns to respond to many forms of external stimuli. Because infants thrive physically and psychologically only in the context of their social relationships, any description of the newborn’s developmental status has to include consideration of the parents’ role as well.

**PARENTAL ROLE IN MOTHER–INFANT ATTACHMENT**

Parenting a newborn infant requires dedication because a newborn’s needs are urgent, continuous, and often unclear. Parents must attend to an infant’s signals and respond empathically. Many factors influence parents’ ability to assume this role.

**Prenatal Factors**

Pregnancy is a period of psychologic preparation for the profound demands of parenting. Women may experience ambivalence, particularly (but not exclusively) if the pregnancy was unplanned. If financial worries, physical illness, prior miscarriages or stillbirths, or other crises interfere with psychologic preparation, the neonate may not be welcomed. For adolescent mothers, the demand that they relinquish their own developmental agenda, such as an active social life, may be especially burdensome.

The early experience of being mothered may establish unconsciously held expectations about nurturing relationships that permit mothers to “tune in” to their infants. These expectations are linked with the quality of later infant–parent interactions. Mothers whose early childhoods were marked by traumatic separations, abuse, or neglect may find it especially difficult to provide consistent, responsive care. Instead, they may reenact their childhood experiences with their own infants, as if unable to conceive of the mother–child relationship in any other way. Bonding may be adversely affected by several risk factors during pregnancy and in the postpartum period that undermine the mother–child relationship and may threaten the infant’s cognitive and emotional development (Table 9-1).

**Social support** during pregnancy, particularly support from the father and close family members, is also important. Conversely, conflict with or abandonment by the father during pregnancy may diminish the mother’s ability to become absorbed with her infant. Anticipation

<table>
<thead>
<tr>
<th>Table 9-1</th>
<th>Prenatal Risk Factors for Attachment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent death of a loved one</td>
<td></td>
</tr>
<tr>
<td>Previous loss of or serious illness in another child</td>
<td></td>
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<tr>
<td>Prior removal of a child</td>
<td></td>
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<tr>
<td>History of depression or serious mental illness</td>
<td></td>
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<tr>
<td>History of infertility or pregnancy loss</td>
<td></td>
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<tr>
<td>Troubled relationship with parents</td>
<td></td>
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<tr>
<td>Financial stress or job loss</td>
<td></td>
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<tr>
<td>Marital discord or poor relationship with the other parent</td>
<td></td>
</tr>
<tr>
<td>Recent move or no community ties</td>
<td></td>
</tr>
<tr>
<td>No friends or social network</td>
<td></td>
</tr>
<tr>
<td>Unwanted pregnancy</td>
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<tr>
<td>No good parenting model</td>
<td></td>
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<tr>
<td>Experience of poor parenting</td>
<td></td>
</tr>
<tr>
<td>Drug and/or alcohol abuse</td>
<td></td>
</tr>
<tr>
<td>Extreme immaturity</td>
<td></td>
</tr>
</tbody>
</table>

From Dixon SD, Stein MT: Encounters with children: pediatric behavior and development, ed 3, St. Louis, 2000, Mosby, p 74.
of an early return to work may make some women reluctant to fall in love with their babies because of anticipated separation. Returning to work should be delayed for at least 6 wk, by which time feeding and basic behavioral adjustments have been established.

Many decisions have to be made by parents in anticipation of the birth of their child. One important choice is that of how the infant will be nourished. Among the important benefits of breastfeeding is its promotion of bonding. Providing breastfeeding education for the parents at the prenatal visit by the pediatrician and by the obstetrician during prenatal care can increase maternal confidence in breastfeeding after delivery and reduce stress during the newborn period (see Chapter 45).

Peripartum and Postpartum Influences
The continuous presence during labor of a woman trained to offer friendly support and encouragement (a doula) results in shorter labor, fewer obstetric complications (including cesarean section), and reduced postpartum hospital stays. Early skin-to-skin contact between mothers and infants immediately after birth may correlate with an increased rate and longer duration of breastfeeding. Most new parents value even a brief period of uninterrupted time in which to get to know their new infant, and increased mother–infant contact over the 1st days of life may improve long-term mother–child interactions. Nonetheless, early separation, although predictably very stressful, does not inevitably impair a mother's ability to bond with her infant. Early discharge from the hospital may undermine bonding, particularly when a new mother is required to resume full responsibility for a busy household.

Postpartum depression may occur in the 1st wk or up to 6 mo after delivery and can adversely affect neonatal growth and development. Screening methods are available for use during neonatal and infant visits to the pediatric provider (Table 9-2). Referral for care will greatly accelerate recovery.

THE INFANT'S ROLE IN MOTHER–INFANT ATTACHMENT
The in utero environment contributes greatly but not completely to the future growth and development of the fetus. Abnormalities in maternal–fetal placental circulation and maternal glucose metabolism or the presence of maternal infection can result in abnormal fetal growth. Infants may be small or large for gestational age as a result. These abnormal growth patterns not only predispose infants to an increased requirement for medical intervention, but also may affect their ability to respond behaviorally to their parents.

Examination of the newborn should include an evaluation of growth and an observation of behavior. The average term newborn weighs approximately 3.4 kg (7.5 lb); boys are slightly heavier than girls. Average weight does vary by ethnicity and socioeconomic status. The average length and head circumference are about 50 cm (20 in) and 35 cm (14 in), respectively, in term infants. Each newborn's growth parameters should be plotted on growth curves specific for that infant's gestational age to determine the appropriateness of size. Likewise specific growth charts for conditions associated with variations in growth patterns have also been developed. The infant's response to being examined may be useful in assessing its vigor, alertness, and tone. Observing how the parents handle their infant, their comfort and affection, is also important. The order of the physical examination should be from the least to the most intrusive maneuver. Assessing visual tracking and response to sound and noting changes of tone with level of activity and alertness are very helpful. Performing this examination and sharing impression with parents is an important opportunity to facilitate bonding (see Chapter 94).

Interactional Abilities
Soon after birth, neonates are alert and ready to interact and nurse. This first alert-awake period may be affected by maternal analgesics and anesthetics or fetal hypoxia. Neonates are nearsighted, having a fixed focal length of 8–12 inches, approximately the distance from the breast to the mother's face, as well as an inborn visual preference for faces. Hearing is well developed, and infants preferentially turn toward a female voice. These innate abilities and predilections increase the likelihood that when a mother gazes at her newborn, the baby will gaze back. The initial period of social interaction, usually lasting about 40 minutes, is followed by a period of somnolence. After that, briefer periods of alertness or excitement alternate with sleep. If a mother misses her baby's first alert-awake period, she may not experience as long a period of social interaction for several days. The hypothalamic–midbrain–limbic–paralimbic–cortical circuit of the parents interact to support responses to the infants that are critical for effective parenting (e.g., emotion, attention, motivation, empathy, and decision making).

Modulation of Arousal
Adaptation to extraterine life requires rapid and profound physiologic changes, including aeration of the lungs, rerouting of the circulation, and activation of the intestinal tract. The necessary behavioral changes are no less profound. To obtain nourishment, to avoid hypo- and hyperthermia, and to ensure safety, neonates must react appropriately to an expanded range of sensory stimuli. Infants must become aroused in response to stimulation, but not so overaroused that their behavior becomes disorganized. Underaroused infants are not able to feed and interact; overaroused infants show signs of autonomic instability, including flushing or mottling, perioral pallor, hiccupping, vomiting, uncontrolled limb movements, and inconsolable crying.

Behavioral States
The organization of infant behavior into discrete behavioral states may reflect an infant's inborn ability to regulate arousal. Six states have been described: quiet sleep, active sleep, drowsy, alert, fussy, and crying. In the alert state, infants visually fixate on objects or faces and follow them horizontally and (within a month) vertically; they also reliably turn toward a novel sound, as if searching for its source. When overstimulated, they may calm themselves by looking away, yawning, or sucking on their lips or hands, thereby increasing parasympathetic activity and reducing sympathetic nervous activity. The behavioral state determines an infant's muscle tone, spontaneous movement, electroencephalogram pattern, and response to stimuli. In active sleep, an infant may show progressively less reaction to a repeated heel stick (habituation), whereas in the drowsy state, the same stimulus may push a child into fussing or crying.

Mutual Regulation
Parents actively participate in an infant's state regulation, alternately stimulating and soothing. In turn, they are regulated by the infant's signals, responding to cries of hunger with a letdown of milk (or with a bottle). Such interactions constitute a system directed toward furthering the infant's physiologic homeostasis and physical growth. At the same time, they form the basis for the emerging psychologic relationship between parent and child. Infants come to associate the presence of the parent with the pleasurable reduction of tension (as in feeding) and show this preference by calming more quickly for their mother than for a stranger. This response, in turn, strengthens a mother's sense of efficacy and her connection with her baby.

IMPLICATIONS FOR THE PEDIATRICIAN
The pediatrician can support healthy newborn development in several ways.

Optimal Practices
A prenatal pediatric visit allows pediatricians to assess potential threats to bonding (a tense spousal relationship) and sources of social support. Supportive hospital policies include the use of birthing rooms rather than operating suites and delivery rooms; encouragement for the father or a trusted relative or friend to remain with the mother during labor or the provision of a professional doula; the practice of giving the newborn infant to the mother immediately after drying and a brief assessment; placement of the newborn in the mother’s room rather
than in a central nursery; and avoiding in-hospital distribution of infant formula. Such policies (“Baby Friendly Hospital”) have been shown to significantly increase breastfeeding rates (see Chapter 94.3). After discharge, home visits by nurses and lactation counselors can reduce early feeding problems and identify emerging medical conditions in either mother or baby. Infants requiring transport to another hospital should be brought to see the mother first, if at all possible. On discharge home, fathers can shield mothers from unnecessary visits and calls and take over household duties, allowing mothers and infants to get to know each other without distractions. The first office visit should occur during the 1st 2 wk after discharge to determine how smoothly the mother and infant are making the transition to life at home. Babies who are discharged early, those who are breastfeeding, and those who are at risk for jaundice should be seen 1-3 days after discharge.

### Assessing Parent–Infant Interactions

During a feeding or when infants are alert and face-to-face with their parents, it is normal for the dyad to appear absorbed in one another. During a feeding or when infants are alert and face-to-face with their parents, it is normal for the dyad to appear absorbed in one another. Babies who become overstimulated by the mother’s voice or activity may turn away or close their eyes, leading to a premature termination of the encounter. Alternatively, the infant may be ready to interact, but the mother may appear preoccupied. Asking a new mother about her own emotional state, and inquiring specifically about a history of depression, facilitates referral for therapy, which may provide long-term benefits to the child. Pediatricians may detect **postpartum depression** using the Edinburgh Postnatal Depression Scale at well-child visits during the 1st yr (see Table 9-2).

#### Table 9-2 Edinburgh Postnatal Depression Scale

<table>
<thead>
<tr>
<th>Response categories</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INSTRUCTIONS FOR USERS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. The mother is asked to underline the response that comes closest to how she has been feeling during the past 7 days.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2. All 10 items must be completed.</td>
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<tr>
<td>3. Care should be taken to avoid the possibility of the mother discussing her answers with others.</td>
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<tr>
<td>4. The mother should complete the scale herself, unless she has limited English or has difficulty with reading.</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. The Edinburgh Postnatal Depression Scale may be used at 6-8 wk to screen postnatal women. The child health clinic, a postnatal checkup, or a home visit may provide a suitable opportunity for its completion.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Edinburgh Postnatal Depression Scale

Name:

Address:

Baby’s age:

Because you have recently had a baby, we would like to know how you are feeling. Please underline the answer that comes closest to how you have felt in the past 7 days, not just how you feel today.

Here is an example, already completed.

I have felt happy:

Yes, all the time

Yes, most of the time

No, not very often

No, not at all

This would mean: “I have felt happy most of the time” during the past week. Please complete the other questions in the same way.

In the past 7 days:

1. I have been able to laugh and see the funny side of things
   - As much as I always could
   - Not quite so much now
   - Definitely not so much now
   - Not at all

2. I have looked forward with enjoyment to things
   - As much as I ever did
   - Rather less than I used to
   - Definitely less than I used to
   - Hardly at all

3. I have blamed myself unnecessarily when things went wrong
   - Yes, most of the time
   - Yes, some of the time
   - Not very often
   - No, never

4. I have been anxious or worried for no good reason
   - No, not at all
   - Hardly ever
   - Yes, sometimes
   - Yes, quite often

5. I have felt scared or panicky for no very good reason
   - Yes, quite a lot
   - Yes, sometimes
   - No, not much
   - No, not at all

6. Things have been getting on top of me
   - Yes, most of the time I haven’t been able to cope at all
   - Yes, sometimes I haven’t been coping as well as usual
   - No, most of the time I have coped quite well
   - No, I have been coping as well as ever

7. I have been so unhappy that I have had difficulty sleeping
   - Yes, most of the time
   - Yes, sometimes
   - Not very often
   - No, not at all

8. I have felt sad or miserable
   - Yes, most of the time
   - Yes, quite often
   - Not very often
   - No, not at all

9. I have been so unhappy that I have been crying
   - Yes, most of the time
   - Yes, quite often
   - Only occasionally
   - No, never

10. The thought of harming myself has occurred to me
    - Yes, quite often
    - Sometimes
    - Hardly ever
    - Never

Response categories are scored 0, 1, 2, and 3 according to increased severity of the symptom. Items marked with an asterisk (*) are reverse scored (i.e., 3, 2, 1, and 0). The total score is calculated by adding the scores for each of the 10 items. Users may reproduce the scale without further permission providing they respect copyright (which remains with the British Journal of Psychiatry) by quoting the names of the authors, the title, and the source of the paper in all reproduced copies.


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Teaching About Individual Competencies

The Newborn Behavior Assessment Scale (NBAS) provides a formal measure of an infant’s neurodevelopmental competencies, including state control, autonomic reactivity, reflexes, habituation, and orientation toward auditory and visual stimuli. This examination can also be used to demonstrate to parents an infant’s capabilities and vulnerabilities. Parents might learn that they need to undress their infant to increase the level of arousal or to swaddle the infant to reduce over-stimulation by containing random arm movements. The NBAS can be
used to support the development of positive early parent-infant relationships. Demonstration of the NBAS to parents in the 1st wk of life has been shown to correlate with improvements in the caretaking environment months later.

*Bibliography is available at Expert Consult.*
Bibliography


The prenatal period and the 1st yr of life provide the platform for remarkable growth and development, setting the trajectory for a child’s life. Neural plasticity, the ability of the brain to be shaped by experience, both positive and negative, is at its peak. Total brain volume doubles in the 1st yr of life and increases by an additional 15% over the 2nd yr. Total brain volume at age 1 mo is approximately 36% of adult volume but by age 1 yr is approximately 72% (83% by 2 yr) (Fig. 10-1). The acquisition of seemingly “simple” skills, such as swallowing, reflect a series of intricate and highly coordinated processes involving multiple levels of neural control distributed among several physiologic systems whose nature and relationships mature throughout the 1st yr of life. Substantial learning of the basic tools of language (phonology, word segmentation) occurs during infancy. Speech processing in older individuals requires defined and precise neuronal networks; the infant brain possesses a structural and functional organization similar to that of adults, suggesting that structural neurologic processing of speech may guide infants to discover the properties of his or her native language. Myelination of the cortex begins at 7-8 mo gestation and continues into adolescence and young adulthood. It proceeds in a posterior to anterior fashion, allowing progressive maturation of sensory, motor, and finally associative pathways. Given the importance of iron, cholesterol, and other nutrients in myelination, adequate stores throughout infancy are critical (see Chapter 45). Inadequate dietary intake, insufficient interactions with caregivers or the wider environment may alter experience-dependent processes that are critical to brain structure development and function during infancy. Although some of these processes may be delayed, as the periods of plasticity close during the rapid developmental changes occurring in infancy, more permanent deficits may result.

The infant acquires new competences in all developmental domains. The concept of developmental trajectories recognizes that complex skills build on simpler ones; it is also important to realize how development in each domain affects functioning in all of the others. All growth parameters should be plotted using the World Heath Organization charts which show how children from birth through 72 mo “should” grow under optimal circumstances (see Figs. 11-1 and 11-2). Table 10-1 presents an overview of key milestones by domain; Table 10-2 presents similar information arranged by age. Table 10-3 presents age at time of appearance on x-ray of centers of ossification. Parents often

seek information about “normal development” during this period and should be directed to reliable sources, including the American Academy of Pediatrics website (www.AAP.org).

**AGE 0-2 MONTHS**

In the full-term infant, myelination is present by the time of birth in the dorsal brainstem, cerebellar peduncles, and posterior limb of the internal capsule. The cerebellar white matter acquires myelin by 1 mo of age. In this period, the infant experiences tremendous growth. Physiologic changes allow the establishment of effective feeding routines and a predictable sleep–wake cycle. The social interactions that occur as parents and infants accomplish these tasks lay the foundation for cognitive and emotional development.

**Physical Development**

A newborn’s weight may initially decrease 10% below birthweight in the 1st wk as a result of excretion of excess extravascular fluid and limited nutritional intake. Nutrition improves as colostrum is replaced by higher-fat breast milk, as infants learn to latch on and suck more efficiently, and as mothers become more comfortable with feeding techniques. Infants regain or exceed birthweight by 2 wk of age and should grow at approximately 30 g (1 oz)/per day during the 1st mo (see Table 15-1). This is the period of fastest postnatal growth. Arms are held to the sides. Limb movements consist largely of uncontrolled writhing, with apparently purposeless opening and closing of the hands. Smiling occurs involuntarily. Eye gaze, head turning, and sucking are under better control and thus can be used to demonstrate infant perception and cognition. An infant’s preferential turning toward the mother’s voice is evidence of recognition memory.

Six behavioral states have been described (see Chapter 9). Initially, as sleep and wakefulness are evenly distributed throughout the 24 hr day (Fig. 10-2). Neurologic maturation accounts for the consolidation of sleep into blocks of 5 or 6 hr at night, with brief awake, feeding periods. Learning also occurs; infants whose parents are consistently more interactive and stimulating during the day learn to concentrate their sleeping during the night.

### Cognitive Development

Infants can differentiate among patterns, colors, and consonants. They can recognize facial expressions (smiles) as similar, even when they appear on different faces. They also can match abstract properties of stimuli, such as contour, intensity, or temporal pattern, across sensory modalities. Infants at 2 mo of age can discriminate rhythmic patterns in native vs non-native language. Infants appear to seek stimuli actively,
as though satisfying an innate need to make sense of the world. These phenomena point to the integration of sensory inputs in the central nervous system. Caretaking activities provide visual, tactile, olfactory, and auditory stimuli; all of these support the development of cognition. Infants habituate to the familiar, attending less to repeated stimuli and increasing their attention to novel stimuli.

### Emotional Development

The infant is dependent on the environment to meet his or her needs. The consistent availability of a trusted adult to meet the infant's urgent needs creates the conditions for secure attachment. Basic trust vs mistrust, the first of Erikson's psychosocial stages (see Chapter 6), depends on attachment and reciprocal maternal bonding. Crying occurs in response to stimuli that may be obvious (a soiled diaper), but are often obscure. Infants who are consistently picked up and held in response to distress cry less at 1 yr and show less-aggressive behavior at 2 yr. Cross-cultural studies show that in societies in which infants are carried close to the mother, babies cry less than in societies in which babies are only periodically carried. Crying normally peaks at about 6 wk of age, when healthy infants may cry up to 3 hr/day; then decreases to 1 hr or less by 3 mo. Infants cry in response to the cry of another infant, which has been interpreted as an early sign of empathy development.

Crying/fussiness is present in 20% of infants younger than 2 mo of age and although in most it is a transient and normal behavioral activity, it is often associated with parental concern and distress. Excessive

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Table 10-2  Emerging Patterns of Behavior During the 1st Yr of Life*

<table>
<thead>
<tr>
<th>PERIOD</th>
<th>Social</th>
<th>Motor</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEONATAL (1ST 4 WK)</td>
<td>Prone: Lies in flexed attitude; turns head from side to side; head sags on ventral suspension</td>
<td>Supine: Generally flexed and a little stiff</td>
</tr>
<tr>
<td></td>
<td>Supine: May fixate face on light in line of vision; “doll’s-eye” movement of eyes on turning of the body</td>
<td>Visual: Moro response active; stepping and placing reflexes; grasp reflex active</td>
</tr>
<tr>
<td></td>
<td>Reflex: May fixate face on light in line of vision; “doll’s-eye” movement of eyes on turning of the body</td>
<td>Social: Visual preference for human face</td>
</tr>
</tbody>
</table>

| AT 1 MO              | Prone: Legs more extended; holds chin up; turns head; head lifted momentarily to plane of body on ventral suspension | Supine: Tonic neck posture predominates; supple and relaxed; head lags when pulled to sitting position |
|                     | Visual: Watches person; follows moving object | Social: Body movements in cadence with voice of other in social contact; beginning to smile |

| AT 2 MO              | Prone: Raises head slightly farther; head sustained in plane of body on ventral suspension | Supine: Tonic neck posture predominates; head lags when pulled to sitting position |
|                     | Visual: Follows moving object 180 degrees | Social: Smiles on social contact; listens to voice and coos |

| AT 3 MO              | Prone: Lifts head and chest with arms extended; head above plane of body on ventral suspension | Supine: Symmetric posture predominates, hands in midline; reaches and grasps objects and brings them to mouth |
|                     | Sitting: Head lag partially compensated when pulled to sitting position; early head control with bobbing motion; back rounded | Standing: When held erect, pushes with feet |
|                     | Reflex: Typical Moro response has not persisted; makes defensive movements or selective withdrawal reactions | Social: Sustained social contact; listens to music; says “aah, ngh” |

| AT 4 MO              | Prone: Lifts head and chest, with head in approximately vertical axis; legs extended | Supine: No head lag when pulled to sitting position; head steady, tipped forward; enjoys sitting with full truncal support |
|                     | Sitting: Head lag partially compensated when pulled to sitting position; early head control with bobbing motion; back rounded | Standing: When held erect, pushes with feet |
|                     | Standing: When held erect, pushes with feet | Adaptive: Seeks raisin, but makes no move to reach for it |
|                     | Social: Laughs out loud; may show displeasure if social contact is broken; excited at sight of food | Social: Seeks raisin, but makes no move to reach for it |

| AT 7 MO              | Prone: Rolls over; pivots or creep-crawls (Knobloch) | Supine: Lifts head; rolls over; squirms |
|                     | Sitting: Sits briefly, with support of pelvis; leans forward on hands; back rounded | Standing: May support most of weight; bounces actively |
|                     | Standing: May support most of weight; bounces actively | Adaptive: Reaches out for and grasps large object; transfers objects from hand to hand; grasp uses radial palm; raises at raisin |
|                     | Standing: When held erect, pushes with feet | Language: Forms polysyllabic vowel sounds |
|                     | Standing: When held erect, pushes with feet | Social: Prefers mother; babbles; enjoys mirror; responds to changes in emotional content of social contact |

| AT 10 MO             | Sitting: Sits up alone and indefinitely without support, with back straight | Supine: Sits briefly, with support of pelvis; leans forward on hands; back rounded |
|                     | Standing: Pulls to standing position; “cruises” or walks holding on to furniture | Standing: May support most of weight; bounces actively |
|                     | Motor: Creeps or crawls | Adaptive: Reaches out for and grasps large object; transfers objects from hand to hand; grasp uses radial palm; raises at raisin |
|                     | Adaptive: Reaches out for and grasps large object; transfers objects from hand to hand; grasp uses radial palm; raises at raisin | Language: Forms polysyllabic vowel sounds |
|                     | Motor: Creeps or crawls | Social: Sustained social contact; listens to music; says “aah, ngh” |

| AT 1 YR              | Motor: Walks with one hand held; rises independently, takes several steps (Knobloch) | Supine: Symmetric posture predominates, hands in midline; reaches and grasps objects and brings them to mouth |
|                     | Motor: Creeps or crawls | Standing: When held erect, pushes with feet |
|                     | Motor: Creeps or crawls | Adaptive: Reaches out for and grasps large object; transfers objects from hand to hand; grasp uses radial palm; raises at raisin |
|                     | Motor: Creeps or crawls | Language: Forms polysyllabic vowel sounds |
|                     | Motor: Creeps or crawls | Social: Prefers mother; babbles; enjoys mirror; responds to changes in emotional content of social contact |

| AT 1 YR              | Motor: Walks with one hand held; rises independently, takes several steps (Knobloch) | Supine: Symmetric posture predominates, hands in midline; reaches and grasps objects and brings them to mouth |
|                     | Motor: Creeps or crawls | Standing: When held erect, pushes with feet |
|                     | Motor: Creeps or crawls | Adaptive: Reaches out for and grasps large object; transfers objects from hand to hand; grasp uses radial palm; raises at raisin |
|                     | Motor: Creeps or crawls | Language: Forms polysyllabic vowel sounds |
|                     | Motor: Creeps or crawls | Social: Prefers mother; babbles; enjoys mirror; responds to changes in emotional content of social contact |

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*Data are derived from those of Gesell (as revised by Knobloch), Shirley, Provence, Wolf, Bailey, and others.

Infants have various signals for their needs and for getting attention from a caregiver. These behaviors progressively increase in intensity in many infants from changes in breathing and color, postural and movement cues, and then to calm vocalizations. These precry cues, if not attended to, will eventually lead to active crying. Some infants may go directly to crying, perhaps based on temperament; these infants may be less easily consolable and may have feeding problems like refusal of feeds. Sensory integration issues may also be involved with the child being over responsive or sensory deprived.

Management of crying/fussiness should include teaching caregivers about precry cues and responding to the signal for feeding in a calm relaxed manner. If sensory overstimulation is a factor, creating a non-distracting, calm environment may help as well as swaddling. When lack of sensory stimulation is present, mother–infant skin-to-skin contact, and carrying the infant may be beneficial. In all situations, reassurance that this is both normal and transient, with only 5% of infants persisting beyond 3 mo of age, helps the family cope.

The emotional significance of any experience depends on both the individual child’s temperament and the parent’s responses (see Table 6-1); differing feeding schedules produce differing reactions. Hunger generates increasing tension; as the urgency peaks, the infant cries the parent offers the breast or bottle and the tension dissipates. Infants fed “on demand” consistently experience this link between their distress, movement cures, and then to calm vocalizations. These precry cues, if not attended to, will eventually lead to active crying. Some infants may go directly to crying, perhaps based on temperament; these infants may be less easily consolable and may have feeding problems like refusal of feeds. Sensory integration issues may also be involved with the child being over responsive or sensory deprived.

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### Table 10-3 Time of Appearance in X-Rays of Centers of Ossification in Infancy and Childhood

<table>
<thead>
<tr>
<th>BOYS—AGE AT APPEARANCE*</th>
<th>BONES AND EPiphyseAL CENTERS</th>
<th>GIRLS—AGE AT APPEARANCE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humerus, head</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carpal bones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 mo ± 5 mo</td>
<td>III</td>
<td>12 mo ± 3 mo</td>
</tr>
<tr>
<td>20 mo ± 5 mo</td>
<td>IV</td>
<td>13 mo ± 3 mo</td>
</tr>
<tr>
<td>23 mo ± 6 mo</td>
<td>V</td>
<td>15 mo ± 4 mo</td>
</tr>
<tr>
<td>26 mo ± 7 mo</td>
<td>I</td>
<td>16 mo ± 5 mo</td>
</tr>
<tr>
<td>32 mo ± 9 mo</td>
<td></td>
<td>18 mo ± 5 mo</td>
</tr>
<tr>
<td>Fingers (epiphyses)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 mo ± 4 mo</td>
<td>Proximal phalanx, 3rd finger</td>
<td>10 mo ± 3 mo</td>
</tr>
<tr>
<td>16 mo ± 4 mo</td>
<td>Proximal phalanx, 2nd finger</td>
<td>11 mo ± 3 mo</td>
</tr>
<tr>
<td>17 mo ± 5 mo</td>
<td>Proximal phalanx, 4th finger</td>
<td>11 mo ± 3 mo</td>
</tr>
<tr>
<td>19 mo ± 7 mo</td>
<td>Distal phalanx, 1st finger</td>
<td>12 mo ± 4 mo</td>
</tr>
<tr>
<td>21 mo ± 5 mo</td>
<td>Proximal phalanx, 5th finger</td>
<td>14 mo ± 4 mo</td>
</tr>
<tr>
<td>24 mo ± 6 mo</td>
<td>Middle phalanx, 3rd finger</td>
<td>15 mo ± 5 mo</td>
</tr>
<tr>
<td>24 mo ± 6 mo</td>
<td>Middle phalanx, 4th finger</td>
<td>15 mo ± 5 mo</td>
</tr>
<tr>
<td>26 mo ± 6 mo</td>
<td>Middle phalanx, 2nd finger</td>
<td>16 mo ± 5 mo</td>
</tr>
<tr>
<td>28 mo ± 6 mo</td>
<td>Distal phalanx, 3rd finger</td>
<td>18 mo ± 4 mo</td>
</tr>
<tr>
<td>28 mo ± 6 mo</td>
<td>Distal phalanx, 4th finger</td>
<td>18 mo ± 5 mo</td>
</tr>
<tr>
<td>32 mo ± 7 mo</td>
<td>Proximal phalanx, 1st finger</td>
<td>20 mo ± 5 mo</td>
</tr>
<tr>
<td>37 mo ± 9 mo</td>
<td>Distal phalanx, 5th finger</td>
<td>23 mo ± 6 mo</td>
</tr>
<tr>
<td>37 mo ± 8 mo</td>
<td>Distal phalanx, 2nd finger</td>
<td>23 mo ± 6 mo</td>
</tr>
<tr>
<td>39 mo ± 10 mo</td>
<td>Middle phalanx, 5th finger</td>
<td>22 mo ± 7 mo</td>
</tr>
<tr>
<td>152 mo ± 18 mo</td>
<td>Sesamoid (adductor pollicis)</td>
<td>121 mo ± 13 mo</td>
</tr>
<tr>
<td>Hip and knee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usually present at birth</td>
<td>Femur, distal</td>
<td>Usually present at birth</td>
</tr>
<tr>
<td></td>
<td>Tibia, proximal</td>
<td>Usually present at birth</td>
</tr>
<tr>
<td>4 mo ± 2 mo</td>
<td>Femur, head</td>
<td>4 mo ± 2 mo</td>
</tr>
<tr>
<td>46 mo ± 11 mo</td>
<td>Patella</td>
<td>29 mo ± 7 mo</td>
</tr>
<tr>
<td>Foot and ankle†</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Values represent mean ± standard deviation, when applicable.

*To nearest month.

†Except for the capitae and hamate bones, the variability of carpal centers is too great to make them very useful clinically.

‡Standards for the foot are available, but normal variation is wide, including some familial variants, so this area is of little clinical use.

The norms present a composite of published data from the Fels Research Institute, Yellow Springs, OH (Pyle SI, Sontag L: Too great to make them very useful clinically. AJR Am J Roentgenol 49:102, 1943), and unpublished data from the Brush Foundation, Case Western Reserve University, Cleveland, OH, and the Harvard School of Public Health, Boston, MA. Compiled by Lieb, Buehl, and Pyle.

Infants with early dysregulation often show increased irritability and physiologic instability (spitting, diarrhea, poor weight gain) as well as later behavioral problems.
Implications for Parents and Pediatricians
Success or failure in establishing feeding and sleep cycles determines parents’ feelings of efficacy. When things go well, the parents’ anxiety and ambivalence, as well as the exhaustion of the early weeks, decrease. Infant issues (colic) or familial conflict will prevent this from occurring. With physical recovery from delivery and hormonal normalization, the mild postpartum depression that affects many mothers passes. If the mother continues to feel sad, overwhelmed, and anxious, the possibility of moderate to severe postpartum depression, found in 10-15% of postpartum women, needs to be considered. Major depression that arises during pregnancy or in the postpartum period threatens the mother–child relationship and is a risk factor for later cognitive and behavioral problems. The pediatrician may be the first professional to encounter the depressed mother and should be instrumental in assisting her in seeking treatment (see Chapter 9).

AGE 2-6 MONTHS
At about age 2 mo, the emergence of voluntary (social) smiles and increasing eye contact mark a change in the parent–child relationship, heightening the parents’ sense of being loved reciprocally. During the next months, an infant’s range of motor and social control and cognitive engagement increases dramatically. Mutual regulation takes the form of complex social interchanges, resulting in strong mutual attachment and enjoyment. Routines are established. Parents are less fatigued.

Physical Development
Between 3 and 4 mo of age, the rate of growth slows to approximately 20 g/day (see Table 15-1 and Figs. 11-1 and 11-2). By age 4 mo, birth weight is doubled. Early reflexes that limited voluntary movement recede. Disappearance of the asymmetric tonic neck reflex means that infants can begin to examine objects in the midline and manipulate them with both hands (see Chapter 590). Waning of the early grasp reflex allows infants both to hold objects and to let them go voluntarily. A novel object may elicit purposeful, although inefficient, reaching. The quality of spontaneous movements also changes, from larger writhing to smaller, circular movements that have been described as “fidgety.” Abnormal or absent fidgety movements may constitute a risk factor for later neurologic abnormalities.

Increasing control of truncal flexion makes intentional rolling possible. Once infants can hold their heads steady while sitting, they can gaze across at things rather than merely looking up at them, opening up a new visual range. They can begin to take food from a spoon. At the same time, maturation of the visual system allows greater depth perception.

In this period, infants achieve stable state regulation and regular sleep–wake cycles. Total sleep requirements are approximately 14-16 hr/24 hr, with about 9-10 hr concentrated at night and 2-3 naps/day. Approximately 70% of infants sleep for a 6-8 hr stretch by age 6 mo (see Fig. 10-2). By 4-6 mo, the sleep electroencephalogram shows a mature pattern, with demarcation of rapid eye movement and 4 stages of non–rapid eye movement sleep. The sleep cycle remains shorter than in adults (50-60 min vs approximately 90 min). As a result, infants arouse to light sleep or wake frequently during the night, setting the stage for behavioral sleep problems (see Chapter 19).

Cognitive Development
The overall effect of these developments is a qualitative change. At 4 mo of age, infants are described as “hatching” socially, becoming interested in a wider world. During feeding, infants no longer focus exclusively on the mother, but become distracted. In the mother’s arms, the infant may literally turn around, preferring to face outward.

Infants at this age also explore their own bodies, staring intently at their hands, vocalizing, blowing bubbles, and touching their ears, cheeks, and genitals. These explorations represent an early stage in the understanding of cause and effect as infants learn that voluntary muscle movements generate predictable tactile and visual sensations. They also have a role in the emergence of a sense of self, separate from the mother. This is the 1st stage of personality development. Infants come to associate certain sensations through frequent repetition. The proprioceptive feeling of holding up the hand and wiggling the fingers always accompanies the sight of the fingers moving. Such self sensations are consistently linked and reproducible at will. In contrast, sensations that are associated with “other” occur with less regularity and in varying combinations. The sound, smell, and feel of the mother sometimes appear promptly in response to crying, but sometimes do not. The satisfaction that the mother or another loving adult provides continues the process of attachment.

Emotional Development and Communication
 Babies interact with increasing sophistication and range. The primary emotions of anger, joy, interest, fear, disgust, and surprise appear in appropriate contexts as distinct facial expressions. When face-to-face, the infant and a trusted adult can match affective expressions (smiling or surprise) approximately 30% of the time. Initiating games (singing, hand games) increases social development. Such face-to-face behavior reveals the infant’s ability to share emotional states, the 1st step in the development of communication. Infants of depressed parents show a different pattern, spending less time in coordinated movement with their parents and making fewer efforts to reengage. Rather than anger, they show sadness and a loss of energy when the parents continue to be unavailable.

Implications for Parents and Pediatricians
Motor and sensory maturation makes infants at 3-6 mo exciting and interactive. Some parents experience their 4 mo old child’s outward turning as a rejection, secretly fearing that their infants no longer love them. For most parents, this is a happy period. Most parents excitedly report that they can hold conversations with their infants, taking turns vocalizing and listening. Pediatricians share in the enjoyment, as the baby coos, makes eye contact, and moves rhythmically. Infants who do not show this reciprocal language and movements are at risk for autism spectrum disorders (see Chapter 30). If this visit does not feel joyful and relaxed, causes such as social stress, family dysfunction, parental mental illness, or problems in the infant–parent relationship should be considered. Parents can be reassured that responding to an infant’s emotional needs cannot spoil the infant. Giving vaccines and drawing blood while the child is seated on the parent’s lap or nursing at the breast increases pain tolerance.

AGE 6-12 MONTHS
With achievement of the sitting position, increased mobility, and new skills to explore the world around them, 6-12 mo old infants show advances in cognitive understanding and communication, and there are new tensions around the themes of attachment and separation. Infants develop will and intentions, characteristics that most parents welcome, but still find challenging to manage.

Physical Development
Growth slows more (see Table 15-1 and Figs. 11-1 and 11-2). By the 1st birthday, birth weight has tripled, length has increased by 50%, and head circumference has increased by 10 cm. The ability to sit unsupported (6-7 mo) and to pivot while sitting (around 9-10 mo) provides increasing opportunities to manipulate several objects at a time and to experiment with novel combinations of objects. These explorations are aided by the emergence of a thumb–finger grasp (8-9 mo) and a neat pincer grasp by 12 mo. Voluntary release emerges at 9 mo. Many infants begin crawling and pulling to stand around 8 mo, followed by cruising. Some walk by 1 yr. Motor achievements correlate with increasing myelination and cerebellar growth. These gross motor skills expand infants’ exploratory range and create new physical dangers, as well as opportunities for learning. Tooth eruption occurs, usually starting with the mandibular central incisors. Tooth development reflects skeletal maturation and bone age, although there is wide individual variation (see Table 10-3 and Chapter 307).

Cognitive Development
The 6 mo old infant has discovered his hands and will soon learn to manipulate objects. At first, everything is mouthed. In time, novel
Infants’ wariness of strangers often makes the 9 mo examination difficult, particularly if the infant is temperamentally prone to react negatively to unfamiliar situations. Initially, the pediatrician should avoid direct eye contact with the child. Time spent talking with the parent and introducing the child to a small, washable toy will be rewarded with more cooperation. The examination can be continued on the parent's lap when feasible.

Bibliography is available at Expert Consult.
Bibliography


The toddler’s newly found ability to walk allows separation and independence; however, the toddler continues to need secure attachment to the parents. At approximately 18 mo of age, the emergence of symbolic thought and language causes a reorganization of behavior, with implications across many developmental domains.

**AGE 12-18 MONTHS**

**Physical Development**

The toddler continues to experience considerable brain growth and myelination in the 2nd yr, resulting in an increase in head circumference of 2 cm over the year (Fig. 11-1; see also Fig. 10-1). Toddlers have relatively short legs and long torsos, with exaggerated lumbar lordosis and protruding abdomens. Growth in length continues at a steady rate (Fig. 11-2).

Most children begin to walk independently at around 12-15 mo of age. Early walking is not associated with advanced development in other domains. Infants initially toddle with a wide-based gait, with the knees bent and the arms flexed at the elbow; the entire torso rotates with each stride; the toes may point in or out, and the feet strike the floor flat. The appearance is that of genu varus (bowleg). Subsequent refinement leads to greater steadiness and energy efficiency. After several months of practice, the center of gravity shifts back and the torso stabilizes, while the knees extend and the arms swing at the sides for balance. The feet are held in better alignment, and the child is able to stop, pivot, and stoop without toppling over (see Chapters 672 and 673).

**Cognitive Development**

Exploration of the environment increases in parallel with improved dexterity (reaching, grasping, releasing) and mobility. Learning follows the precepts of Piaget’s sensorimotor stage (see Chapter 6). Toddlers manipulate objects in novel ways to create interesting effects, such as stacking blocks or putting things into a computer disk drive. Playthings are also more likely to be used for their intended purposes (combs for hair, cups for drinking). Imitation of parents and older siblings or other children is an important mode of learning. Make-believe (symbolic) play centers on the child’s own body (pretending to drink from an empty cup) (Table 11-1; also see Table 10-1).

**Emotional Development**

Infants who are approaching the developmental milestone of taking their first steps may be irritable. Once they start walking, their predominant mood changes markedly. Toddlers are described as “intoxicated” or “giddy” with their new ability and with the power to control the distance between themselves and their parents. Exploring toddlers orbit around their parents, moving away and then returning for a reassuring touch before moving away again. A securely attached child will

*Text continued on p. 75*
Birth to 24 months: Boys
Head circumference-for-age and
Weight-for-length percentiles

NAME ________________________________
RECORD # ______________________________

Figure 11-1 The World Health Organization Growth Charts. Weight/length and head circumference for boys (A) and girls (B). (Courtesy of the World Health Organization: WHO Child Growth Standards, 2014. http://www.who.int/childgrowth/standards/en/)

Continued
Birth to 24 months: Girls
Head circumference-for-age and
Weight-for-length percentiles

Published by the Centers for Disease Control and Prevention, November 1, 2009

Figure 11-1, cont’d
Birth to 24 months: Girls
Length-for-age and Weight-for-age percentiles

NAME ____________________________

Published by the Centers for Disease Control and Prevention, November 1, 2009

Figure 11-2, cont’d
### Emerging Patterns of Behavior from 1-5 Yr of Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Motor</th>
<th>Adaptive</th>
<th>Language</th>
<th>Social</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 MO</td>
<td>Walks alone; crawls up stairs</td>
<td>Makes tower of 3 cubes; makes a line with crayon; inserts raisin in bottle</td>
<td>Jargon; follows simple commands; may name a familiar object (e.g., ball); responds to his/her name</td>
<td>Indicates some desires or needs by pointing; hugs parents</td>
</tr>
<tr>
<td>18 MO</td>
<td>Runs stiffly; sits on small chair; walks up stairs with 1 hand held; explores drawers and wastebaskets</td>
<td>Makes tower of 4 cubes; imitates scribbling; imitates vertical stroke; dumps raisin from bottle</td>
<td>10 words (average); names pictures; identifies 1 or more parts of body</td>
<td>Feeds self; seeks help when in trouble; may complain when wet or soiled; kisses parent with puckering</td>
</tr>
<tr>
<td>24 MO</td>
<td>Runs well, walks up and down stairs, 1 step at a time; opens doors; climbs on furniture; jumps</td>
<td>Makes tower of 7 cubes (a 21 mo); scribbles in circular pattern; imitates horizontal stroke; folds paper once imitatively</td>
<td>Puts 3 words together (subject, verb, object)</td>
<td>Handles spoon well; often tells about immediate experiences; helps to undress; listens to stories when shown pictures</td>
</tr>
<tr>
<td>30 MO</td>
<td>Goes up stairs alternating feet</td>
<td>Makes tower of 9 cubes; makes vertical and horizontal strokes, but generally will not join them to make cross; imitates circular stroke, forming closed figure</td>
<td>Refers to self by pronoun “I”; knows full name</td>
<td>Helps put things away; pretends in play</td>
</tr>
<tr>
<td>36 MO</td>
<td>Rides tricycle; stands momentarily on 1 foot</td>
<td>Makes tower of 10 cubes; imitates construction of “bridge” of 3 cubes; copies circle; imitates cross</td>
<td>Knows age and sex; counts 3 objects correctly; repeats 3 numbers or a sentence of 6 syllables; most of speech intelligible to strangers</td>
<td>Plays simple games (in “parallel” with other children); helps in dressing (unbuttons clothing and puts on shoes); washes hands</td>
</tr>
<tr>
<td>48 MO</td>
<td>Hops on 1 foot; throws ball overhand; uses scissors to cut out pictures; climbs well</td>
<td>Copies bridge from model; imitates construction of “gate” of 5 cubes; copies cross and square; draws man with 2-4 parts besides head; identifies longer of 2 lines</td>
<td>Counts 4 pennies accurately; tells story</td>
<td>Plays with several children, with beginning of social interaction and role-playing; goes to toilet alone</td>
</tr>
<tr>
<td>60 MO</td>
<td>Skips</td>
<td>Draws triangle from copy; names heavier of 2 weights</td>
<td>Names 4 colors; repeating sentence of 10 syllables; counts 10 pennies correctly</td>
<td>Dresses and undresses; asks questions about meaning of words; engages in domestic role-playing</td>
</tr>
</tbody>
</table>

*Data derived from those of Gesell (as revised by Knobloch), Shirley, Provence, Wolf, Bailey, and others. After 6 yr, the Wechsler Intelligence Scales for Children (WISC-IV) and other scales offer the most precise estimates of developmental level. To have their greatest value, they should be administered only by an experienced and qualified person.*

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use the parent as a secure base from which to explore independently. Proud of her or his accomplishments, the child illustrates Erikson’s stage of autonomy and separation (see Chapter 6). The toddler who is overly controlled and discouraged from active exploration will feel doubt, shame, anger, and insecurity. All children will experience tantrums, reflecting their inability to delay gratification, suppress or displace anger, or verbally communicate their emotional states. The quality of the parent–child relationship may moderate negative effects of child care arrangements when parents work.

### Linguistic Development

Receptive language precedes expressive language. By the time infants speak their first words around 12 mo of age, they already respond appropriately to several simple statements, such as “no,” “bye-bye,” and “give me.” By 15 mo, the average child points to major body parts and uses 4-6 words spontaneously and correctly. Toddlers also enjoy polysyllabic jargon (see Tables 10-1 and 11-1), but do not seem upset that no one understands. Most communication of wants and ideas continues to be nonverbal.

### Implications for Parents and Pediatricians

Parents who cannot recall any other milestone tend to remember when their child began to walk, perhaps because of the symbolic significance of walking as an act of independence and/or because of the new demands that the ambulating toddler places on his or her parent. All toddlers should be encouraged to explore their environments; a child’s ability to wander out of sight also increases the risks of injury and the need for supervision.

In the office setting, many toddlers are comfortable exploring the examination room, but cling to the parents under the stress of the examination. Performing most of the physical examination in the parent’s lap may help allay fears of separation. Infants who become more, not less, distressed in their parents’ arms or who avoid their parents at times of stress may be insecurely attached. Young children who, when distressed, turn to strangers rather than parents for comfort are particularly worrisome. Children raised in “toxic” stressful environments have increased vulnerability to disease. The conflicts between independence and security manifest in issues of discipline, temper tantrums, toilet training, and changing feeding behaviors. Parents should be counseled on these matters within the framework of normal development.

Parents may express concern about poor food intake as growth slows. The growth chart should provide reassurance. Most children still take two daytime naps, although the duration steadily decreases (see Fig. 10-1).

### AGE 18-24 MONTHS

#### Physical Development

Motor development during this period is reflected in improvements in balance and agility and the emergence of running and stair climbing. Height and weight increase at a steady rate during this year, with a gain of 5 in and 5 lb. By 24 mo, children are about half of their ultimate adult height. Head growth slows slightly. Eighty-five percent of adult head circumference is achieved by age 2 yr, with just an additional 5 cm gain over the next few years (see Fig. 11-1 and Table 15-1).

#### Cognitive Development

At approximately 18 mo of age, several cognitive changes coalesce, marking the conclusion of the sensory-motor period. These can be observed during self-initiated play. Object permanence is firmly established; toddlers anticipate where an object will end up, even though the object was not visible while it was being moved. Cause and effect are better understood, and toddlers demonstrate flexibility in problem solving (e.g., using a stick to obtain a toy that is out of reach, figuring out how to wind a mechanical toy). Symbolic transformations in play are no longer tied to the toddler’s own body, so that a doll can be “fed” from an empty plate. Like the reorganization that occurs at 9 mo (see Chapter 10), the cognitive changes at 18 mo correlate with important changes in the emotional and linguistic domains (see Table 11-1).
**Emotional Development**

The relative independence of the preceding half-year often gives way to increased clingingness around 18 mo. This stage, described as “raprochement,” may be a reaction to growing awareness of the possibility of separation. Many parents report that they cannot go anywhere without having a small child attached to them. **Separation anxiety** will be manifest at bedtime. Many children use a special blanket or stuffed toy as a **transitional object**, which functions as a symbol of the absent parent. The transitional object remains important until the transition to symbolic thought has been completed and the symbolic presence of the parent has been fully internalized. Despite the attachment to the parent, the child’s use of “no” is a way of declaring independence. Individual differences in temperament, in both the child and the parents play a critical role in determining the balance of conflict vs cooperation in the parent–child relationship. As effective language emerges, conflicts become less frequent.

Self-conscious awareness and internalized standards of behavior first appear at this age. Toddlers looking in a mirror will, for the first time, reach for their own face rather than the mirror image if they notice something unusual on their nose. They begin to recognize when toys are broken and may hand them to their parents to fix. Language becomes a means of impulse control, early reasoning, and connection between ideas. When tempted to touch a forbidden object, they may tell themselves “no, no.” This is the very beginning of the formation of a conscience. The fact that they often go on to touch the object anyway demonstrates the relative weakness of internalized inhibitions at this stage.

**Linguistic Development**

Perhaps the most dramatic developments in this period are linguistic. Labeling of objects coincides with the advent of symbolic thought. After the realization that words can stand for things occurs, a child’s vocabulary balloons from 10-15 words at 18 mo to between 50 and 100 at 2 yr. After acquiring a vocabulary of about 50 words, toddlers begin to combine them to make simple sentences, the beginning of grammar. At this stage, toddlers understand 2-step commands, such as “Give me the ball and then get your shoes.” Language also gives the toddler a sense of control over the surroundings, as in “night-night” or “bye-bye.” The emergence of verbal language marks the end of the sensory-motor period. As toddlers learn to use symbols to express ideas and solve problems, the need for cognition based on direct sensation and motor manipulation wanes.

**Implications for Parents and Pediatricians**

With children’s increasing mobility, physical limits on their explorations become less effective; words become increasingly important for behavior control as well as cognition. Children with delayed language acquisition often have greater behavior problems and frustrations due to problems with communication. Language development is facilitated when parents and caregivers use clear, simple sentences; ask questions; and respond to children’s incomplete sentences and gestural communication with the appropriate words. Television viewing, as well as television as background noise, decreases parent–child verbal interactions, whereas looking at picture books and engaging the child in 2-way conversations stimulate language development.

In the office setting, certain procedures may lessen the child’s **stranger anxiety**. Avoid direct eye contact initially. Perform as much of the examination as feasible with the child on the parent’s lap. Pediatricians can help parents understand the resurgence of problems with separation and the appearance of a treasured blanket or teddy bear as a developmental phenomenon. Parents must understand the importance of exploration. Rather than limiting movement, parents should place toddlers in safe environments or substitute 1 activity for another. Methods of discipline, including corporal punishment, should be discussed; effective alternatives will usually be appreciated. Helping parents to understand and adapt to their children’s different temperamental styles can constitute an important intervention (see Table 6-1). Developing daily routines is helpful to all children at this age. Rigidity in those routines reflects a need for mastery over a changing environment.

*Bibliography is available at Expert Consult.*
Bibliography
The emergence of language and exposure of children to an expanding social sphere represent the critical milestones for children ages 2-5 yr. As toddlers, children learn to walk away and come back to the secure adult or parent. As preschoolers, they explore emotional separation, alternating between stubborn opposition and cheerful compliance, between bold exploration and clinging dependence. Increasing time spent in classrooms and playgrounds challenges a child's ability to adapt to new rules and relationships. Emboldened by their growing array of new skills and accomplishments, preschool children also are increasingly cognizant of the constraints imposed on them by the adult world and their own limited abilities.

**STRUCTURAL DEVELOPMENT OF THE BRAIN**

The preschool brain experiences dramatic changes in its anatomical and physiologic characteristics, with increases in cortical area, decreases in cortical thickness, and changing cortical volume. These changes are not uniform across the brain, but vary by region. Gray and white matter tissue properties change dramatically, including diffusion properties in the major cerebral fiber tracts. Dramatic increases occur in the brain metabolic demands. In general, a greater number of brain regions are required among younger compared to older children to complete the same cognitive task. This duplication has been interpreted as a form of "scaffolding," which is discarded with increasing age. The preschool brain is characterized by growth and expansion, that will be followed in later years by pruning.

**PHYSICAL DEVELOPMENT**

Somatic and brain growth slows by the end of the 2nd yr of life, with corresponding decreases in nutritional requirements and appetite, and the emergence of "picky" eating habits (see Table 15-1). Increases of approximately 2 kg (4-5 lb) in weight and 7-8 cm (2-3 in) in height per year are expected. Birthweight quadruples by 2.5 yr of age. An average 4 yr old weighs 40 lb and is 40 in tall. The head will grow only an additional 5-6 cm between ages 3 and 18 yr. Current growth charts, with growth parameters, can be found on the Centers for Disease Control and Prevention website (http://www.cdc.gov/growthcharts/) and in Chapter 15. Children with early adiposity rebound (increase in body mass index) are at increased risk for adult obesity.

Growth of sexual organs is commensurate with somatic growth. The preschooler has genu valgum (knock-knees) and mild pes planus (flatfoot). The torso slims as the legs lengthen. Physical energy peaks, and the need for sleep declines to 11-13 hr/24 hr, with the child eventually dropping the nap (see Fig. 10-1). Visual acuity reaches 20/30 by age 3 yr and 20/20 by age 4 yr. All 20 primary teeth have erupted by 3 yr of age (see Chapter 307).

Most children walk with a mature gait and run steadily before the end of their 3rd yr (see Table 11-1). Beyond this basic level, there is wide variation in ability as the range of motor activities expands to include throwing, catching, and kicking balls; riding on bicycles; climbing on playground structures; dancing; and other complex pattern behaviors. Stylistic features of gross motor activity, such as
tempo, intensity, and cautiousness, also vary significantly. Although toddlers may walk with different styles, toe walking should not persist.

The effects of such individual differences on cognitive and emotional development depend in part on the demands of the social environment. Energetic, coordinated children may thrive emotionally with parents or teachers who encourage physical activity; lower-energy, more cerebral children may thrive with adults who value quiet play.

**Handedness** is usually established by the 3rd yr. Frustration may result from attempts to change children's hand preference. Variations in fine-motor development reflect both individual proclivities and different opportunities for learning. Children who are restricted from drawing with crayons, for example, develop a mature pencil grasp later.

**Bowel and bladder control** emerge during this period, with "readiness" for toileting having large individual and cultural variation. Girls tend to train faster and earlier than boys. Bed-wetting is normal up to age 4 yr in girls and age 5 yr in boys (see Chapter 23.3). Many children master toileting with ease, particularly once they are able to verbalize their bodily needs. For others, toilet training can involve a protracted power struggle. Refusal to defecate in the toilet or potty is relatively common and can lead to constipation and parental frustration. Defusing the issue with a temporary cessation of training (and a return to diapers) often allows toilet mastery to proceed.

**Implications for Parents and Pediatricians**

The normal decrease in appetite at this age may cause parental concern about nutrition; growth charts should reassure parents that the child’s intake is adequate. Children normally modulate their food intake to match their somatic needs according to feelings of hunger and satiety. Daily intake fluctuates, at times widely, but intake during the period of a week is relatively stable. A complete multivitamin can be used to assure adequate vitamin and mineral intake. Parents should provide a predictable eating schedule, with 3 meals and 2 snacks per day, allowing the child to choose how much to eat.

Highly active children face increased risks of injury, and parents should be counseled about safety precautions. Parental concerns about possible hyperactivity may reflect inappropriate expectations, heightened fears, or true overactivity. Children who engage in impulsive activity with no apparent regard for personal safety should be evaluated further.

**LANGUAGE, COGNITION, AND PLAY**

These 3 domains all involve symbolic function, a mode of dealing with the world that emerges during the preschool period.

**Language**

Our understanding of the acquisition of language is evolving. Preschool children command significant computational skills and understanding of statistical patterns that allow them to learn about both language and causation. The 2 and 3 yr old child employs frequency distributions to identify phonetic units distinguishing words in his or her native language from other languages.

Language development occurs most rapidly between 2 and 5 yr of age. Vocabulary increases from 50-100 words to more than 2,000. Sentence structure advances from telegraphic phrases ("Baby cry") to sentences incorporating all of the major grammatical components. As a rule of thumb, between the ages of 2 and 5 yr, the number of words in a typical sentence equals the child’s age (2 by age 2 yr, 3 by age 3 yr, and so on). By 21-24 mo, most children are using possessives ("My ball"), progressives (the "-ing" construction, as in "I playing"), questions, and negatives. By age 4 yr, most children can count to 4 and use the past tense; by age 5 yr, they can use the future tense. Children do not use figurative speech; they will only comprehend the literal speech; they abstract the complex rules of grammar from the ambient language, generating implicit hypotheses. Evidence for the existence of such implicit rules comes from analysis of grammatical errors, such as the overgeneralized use of "-s" to signify the plural and "-ed" to signify the past ("We seed lots of mouses.").

Language is linked to both cognitive and emotional development. Language delays may be the first indication that a child has an intellectual disability, has an autism spectrum disorder, or has been maltreated. Language plays a critical part in the regulation of behavior through internalized "private speech" in which a child repeats adult prohibitions, first audibly and then mentally. Language also allows children to express feelings, such as anger or frustration, without acting them out; consequently, language-delayed children show higher rates of tantrums and other externalizing behaviors.

Preschool language development lays the foundation for later success in school. Approximately 35% of children in the United States may enter school lacking the language skills that are the prerequisites for acquiring literacy. Children from socially and economically disadvantaged backgrounds have an increased risk of school problems, making early detection, along with referral and enrichment, important. Although children typically learn to read and write in elementary school, critical foundations for literacy are established during the preschool years. Through repeated early exposure to written words, children learn about the uses of writing (telling stories or sending messages) and about its form (left to right, top to bottom). Early errors in writing, like errors in speaking, reveal that literacy acquisition is an active process involving the generation and revision of hypotheses. Programs such as Head Start are especially important for improving language skills for children from bilingual homes. Such parents should be reassured that although bilingual children do initially lag behind their monolingual peers in acquiring language, they learn the differing rules governing both languages. Bilingual children do not follow the same course of language development as monolingual children, but create a different system of language cues. Several cognitive advantages have been repeatedly demonstrated among bilingual compared to monolingual children.

Picture books have a special role not only in familiarizing young children with the printed word but also in the development of verbal language. Children's vocabulary and receptive language improve when their parents or caregivers consistently read to them. Reading aloud with a young child is an interactive process in which a parent repeatedly focuses the child's attention on a particular picture, asks questions, and then gives the child feedback (dialogic reading). The elements of shared attention, active participation, immediate feedback, repetition, and graduated difficulty make such routines ideal for language learning. Programs in which physicians provide books to preschool children have shown improvement in language skills among the children.

The period of rapid language acquisition is also when **developmental dysfluency** and **stuttering** are most likely to emerge; these can be traced to activation of the cortical motor, sensory, and cerebellar areas. Common difficulties include pauses and repetitions of initial sounds. Stress or excitement exacerbates these difficulties, which generally resolve on their own. Although 5% of preschool children will stutter, it will resolve in 80% of those children by age 8 yr. Children with stuttering should be referred for evaluation if it is severe, persistent, or associated with anxiety, or if parental concern is elicited. **Treatment** includes guidance to parents to reduce pressures associated with speaking.

Language acquisition depends critically on environmental input. Key determinants include the amount and variety of speech directed toward children and the frequency with which adults ask questions and encourage verbalization. Children raised in poverty typically perform lower on measures of language development compared to children from economically advantaged families.

Although experience influences the rate of language development, many linguists believe that the basic mechanism for language learning is "hard-wired" in the brain. Children do not simply imitate adult speech; they abstract the complex rules of grammar from the ambient language, generating implicit hypotheses. Evidence for the existence of such implicit rules comes from analysis of grammatical errors, such as the overgeneralized use of "-s" to signify the plural and "-ed" to signify the past ("We seed lots of mouses.").

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Cognition
The preschool period corresponds to Piaget’s preoperational (prelogical) stage, characterized by magical thinking, egocentrism, and thinking that is dominated by perception, not abstraction (see Table 6-2). Magical thinking includes confusing coincidence with causality, animism (attributing motivations to inanimate objects and events), and unrealistic beliefs about the power of wishes. A child might believe that people cause it to rain by carrying umbrellas, that the sun goes down because it is tired, or that feeling resentment toward a sibling can actually make that sibling sick. Egocentrism refers to a child’s inability to take another’s point of view and does not connote selfishness. A child might try to comfort an adult who is upset by bringing the adult a favorite stuffed animal. After 2 yr of age, the child develops a concept of herself or himself as an individual and senses the need to feel “whole.”

Piaget demonstrated the dominance of perception over logic. In one experiment, water is poured back and forth between a tall, thin vase and a low, wide dish, and children are asked which container has more water. Invariably, they choose the one that looks larger (usually the tall vase), even when the examiner points out that no water has been added or taken away. Such misunderstandings reflect young children’s developing hypotheses about the nature of the world as well as their difficulty in attending simultaneously to multiple aspects of a situation.

Recent work indicating that preschool children do have the ability to understand causal relationships has modified our understanding of the ability of preschool children to engage in abstract thinking. (see Chapter 7)

Imitation, central to the learning experience of preschool children, is now being recognized as a complex act because of the differences in the size of the operators (the adult and the child), different levels of dexterity, and even different outcomes. A child who watches an adult unsuccessfully attempt a simple act (unscrew a lid) will imitate the action—but often with the intended outcome, not the demonstrated but failed outcome. Thus “imitation” goes beyond the mere repetition of observed movements.

By age 3, children have self-identified their sex, and are actively seeking understanding of the meaning of gender identification. There is a developmental progression from rigidity (boys and girls have strict gender roles) in the early preschool years to a more flexible realistic understanding (boys and girls can have a variety of interests).

Play
Play involves learning, physical activity, socialization with peers, and practicing adult roles. Play increases in complexity and imagination, from simple imitation of common experiences, such as shopping and putting baby to bed (2 or 3 yr of age), to more extended scenarios involving singular events, such as going to the zoo or going on a trip (3 or 4 yr of age), to the creation of scenarios that have only been imagined, such as flying to the moon (4 or 5 yr of age). By age 3 yr, cooperative play is seen in activities such as building a tower of blocks together; later, more structured role-play activity, as in playing house, is seen. Play also becomes increasingly governed by rules, from early rules about asking (rather than taking) and sharing (2 or 3 yr of age), to rules that change from moment to moment, according to the desires of the players (4 and 5 yr of age), to the beginning of the recognition of rules as relatively immutable (5 yr of age). Electronic forms of play (games) are best if interactive and educational.

Play also allows for resolution of conflicts and anxiety and for creative outlets. Children can vent anger safely (spanking a doll), take on superpowers (dinosaur and superhero play), and obtain things that are denied in real life (a make-believe friend or stuffed animal). Creativity is particularly apparent in drawing, painting, and other artistic activities. Themes and emotions that emerge in a child’s drawings often reflect the emotional issues of greatest importance for the child.

Difficulty distinguishing fantasy from reality colors a child’s perception of what the child views in the media, through programming and advertising. One fourth of young children have a television set in their bedroom; a TV in the bedroom is associated with more hours of watching. The number of hours that preschoolers watch TV exceeds guide-lines. Interactive quality educational programming in which children develop social relationships with the characters can increase learning. However, exposure to commercial television with violent content is associated with later behavior problems and because children younger than 8 yr are not able to comprehend the concept of persuasive intent, they are more vulnerable to television advertising.

Implications for Parents and Pediatricians
The significance of language as a target for assessment and intervention cannot be overestimated because of its central role as an indicator of cognitive and emotional development and a key factor in behavioral regulation and later school success. As language emerges, parents can support emotional development by using words that describe the child’s feeling states (“You sound angry right now:”) and urging the child to use words to express, rather than act out, feelings. Active imaginations will come into play when children offer explanations for misbehavior. A parent’s best way of dealing with untruths is to address the event, not the child, and have the child participate in making things right.

Parents should have a regular time each day for reading or looking at books with their children. Programs such as Reach Out and Read, in which pediatricians give out picture books along with appropriate guidance during primary care visits, have been effective in increasing reading aloud and thereby promoting language development, particularly in lower-income families. Television and similar media should be limited to 2 hr/day of quality programming, and parents should be watching the programs with their children and debriefing their young children afterward. At-risk children, particularly those living in poverty, can better meet future school challenges if they have early high-quality experiences, such as Head Start.

Preoperational thinking constrains how children understand experiences of illness and treatment. Children begin to understand that bodies have “insides” and “outsides.” Children should be given simple, concrete explanations for medical procedures and given some control over procedures if possible. Children should be reassured that they are not to blame when receiving a vaccine or venipuncture. An adhesive bandage will help to make the body whole again in a child’s mind.

The active imagination that fuels play and the magical, animist thinking characteristic of preoperational cognition can also generate intense fears. More than 80% of parents report at least 1 fear in their preschool children. Refusal to take baths or to sit on the toilet may arise from the fear of being washed or flushed away, reflecting a child’s immature appreciation of relative size. Attempts to demonstrate rationally that there are no monsters in the closet often fail, inasmuch as the fear arises from prereational thinking. However, this same thinking allows parents to be endowed with magical powers that can banish the monsters with “monster spray” or a night light. Parents should acknowledge the fears, offer reassurance and a sense of security, and give the child some sense of control over the situation. Use of the Draw-a-Person, in which a child is asked to draw the best person the child can, may help elucidate a child’s viewpoint.

EMOTIONAL AND MORAL DEVELOPMENT
Emotional challenges facing preschool children include accepting limits while maintaining a sense of self-direction, reining in aggressive and sexual impulses, and interacting with a widening circle of adults and peers. At 2 yr of age, behavioral limits are predominantly external; by 5 yr of age, these controls need to be internalized if a child is to function in a typical classroom. Success in achieving this goal relies on prior emotional development, particularly the ability to use internalized images of trusted adults to provide a secure environment in times of stress. The love a child feels for important adults is the main incentive for the development of self-control.

Children learn what behaviors are acceptable and how much power they wield vis-à-vis important adults by testing limits. Testing increases when it elicits attention, even though that attention is often negative, and when limits are inconsistent. Testing often arouses parental anger or inappropriate solicitude as a child struggles to separate, and it gives rise to a corresponding parental challenge: letting go. Excessively tight
limits can undermine a child’s sense of initiative, whereas overly loose limits can provoke anxiety in a child who feels that no one is in control. Control is a central issue. Young children cannot control many aspects of their lives, including where they go, how long they stay, and what they take home from the store. They are also prone to lose internal control, that is, to have temper tantrums. Fear, overtiredness, inconsistent expectations, or physical discomfort can also evoke tantrums. Tantrums normally appear toward the end of the 1st yr of life and peak in prevalence between 2 and 4 yr of age. Tantrums lasting more than 15 min or regularly occurring more than 3 times/day may reflect underlying medical, emotional, or social problems.

Preschool children normally experience complicated feelings toward their parents that can include strong attachment and possessiveness toward the parent of the opposite sex, jealousy and resentment of the other parent, and fear that these negative feelings might lead to abandonment. These emotions, most of which are beyond a child’s ability to comprehend or verbalize, often find expression in highly labile moods. The resolution of this crisis (a process extending over years) involves a child’s unspoken decision to identify with the parents rather than compete with them. Play and language foster the development of emotional controls by allowing children to express emotions and role play.

Curiosity about genitals and adult sexual organs is normal, as is masturbation. Excessive masturbation interfering with normal activity, acting out sexual intercourse, extreme modesty, or mimicry of adult seductive behavior all suggests the possibility of sexual abuse or inappropriate exposure (see Chapter 40.1). Modesty appears gradually between 4 and 6 yr of age, with wide variations among cultures and families. Parents should begin to teach children about “private” body areas before school entry.

Morality is constrained by a child’s cognitive level and language abilities, but develops as the child continues her or his identity with the parents. Beginning before the 2nd birthday, the child’s sense of right and wrong stems from the desire to earn approval from the parents and avoid negative consequences. The child’s impulses are tempered by external forces; the child has not yet internalized societal rules or a sense of justice and fairness. Over time, as the child internalizes parental admonitions, words are substituted for aggressive behaviors. Finally, the child accepts personal responsibility. Actions will be viewed by damage caused, not by intent. Empathic responses to others’ distress arise during the 2nd yr of life, but the ability to consider another child’s point of view remains limited throughout this period. In keeping with a child’s inability to focus on more than 1 aspect of a situation at a time, fairness is taken to mean equal treatment, regardless of circumstance. A 4 yr old will acknowledge the importance of taking turns, but will complain if he or she didn’t get enough time. Rules tend to be absolute, with guilt assigned for bad outcomes, regardless of intentions.

Implications for Parents and Pediatricians

The importance of the preschooler’s sense of control over his or her body and surroundings has implications for practice. Preparing the patient by letting the child know how the visit will proceed is reassuring. Tell the child what will happen, but don’t ask permission unless you are willing to deal with a “no” answer. A brief introduction to “private parts” is warranted before the genital examination.

The visit of the 4 or 5 yr old should be entertaining, because of the child’s ability to communicate, as well as the child’s natural curiosity. Physicians should realize that all children are occasionally difficult. Guidance emphasizing appropriate expectations for behavioral and emotional development and acknowledging normal parental feelings of anger, guilt, and confusion should be part of all visits at this time. Parents should be queried about daily routines and their expectations of child behavior. Providing children with choices (all options being acceptable to the parent) and encouraging independence in self-care activities (feeding, dressing, and bathing) will reduce conflicts.

Although some cultures condone the use of corporal punishment for disciplining of young children, it is not an effective means of behavioral control. As children habituate to repeated spanking, parents have to spank ever harder to get the desired response, increasing the risk of serious injury. Sufficiently harsh punishment may inhibit undesired behaviors, but at great psychologic cost. Children mimic the corporal punishment that they receive; children who are spanked will have more aggressive behaviors later. Whereas spanking is the use of force, externally applied, to produce behavior change, discipline is the process that allows the child to internalize controls on behavior. Alternative discipline strategies should be offered, such as the “countdown,” along with consistent limit setting, clear communication of rules, and frequent approval. Discipline should be immediate, specific to the behavior, and time-limited. Time-out for approximately 1 min/yr of age is very effective. A kitchen timer allows the parent to step back from the situation; the child is free when the timer rings.

Bibliography is available at Expert Consult.
Bibliography

Richert RA, Robb MB, Smith EI: Media as social partners: the social nature of young children’s learning from screen media, Child Dev 82:82–95, 2011.
Middle childhood (6-11 yr of age) is the period in which children increasingly separate from parents and seek acceptance from teachers, other adults, and peers. Children begin to feel under pressure to conform to the style and ideals of the peer group. Self-esteem becomes a central issue, as children develop the cognitive ability to consider their own self-evaluations and their perception of how others see them. For the first time, they are judged according to their ability to produce socially valued outputs, such as getting good grades, playing a musical instrument, or hitting home runs.

**PHYSICAL DEVELOPMENT**

Growth occurs discontinuously, in 3-6 irregularly timed spurts each year, but varies both within and among individuals. Growth during the period averages 3-3.5 kg (6.6-7.7 lb) and 6-7 cm (2.4-2.8 in) per year (Fig. 13-1). The head grows only 2 cm in circumference throughout the entire period, reflecting a slowing of brain growth. Myelinization continues into adolescence, with peak gray matter at 12-14 yr. Body habitus is more erect than previously, with long legs compared with the torso.

Growth of the midface and lower face occurs gradually. Loss of deciduous (baby) teeth is a more dramatic sign of maturation, beginning around 6 yr of age. Replacement with adult teeth occurs at a rate of about 4 per year, so that by age 9 yr, children will have 8 permanent incisors and 4 permanent molars. Premolars erupt by 11-12 yr of age (see Chapter 307). Lymphoid tissues hypertrophy, often giving rise to impressive tonsils and adenoids.

Muscular strength, coordination, and stamina increase progressively, as does the ability to perform complex movements, such as dancing or shooting baskets. Such higher-order motor skills are the result of both maturation and training; the degree of accomplishment reflects wide variability in innate skill, interest, and opportunity.

Physical fitness has declined among school-age children. Sedentary habits at this age are associated with increased lifetime risk of obesity, cardiovascular disease, academic achievement, and lower self-esteem (see Chapter 47). The number of overweight children and the degree of overweightness have been increasing, although recently at a slower rate (see Chapter 47). Only 15% of middle and junior high schools require physical education class at least 3 days/wk. One quarter of youth do not engage in any free-time physical activity, despite the recommendation for 1 hr of physical activity per day.

Perceptions of body image develop early during this period; children as young as 5 and 6 yr express dissatisfaction with their body image; by ages 8 and 9 yr many of these youth report trying to diet, often using
Figure 13-1 Stature (height) for age and weight for boys (A) and girls (B) ages 2 to 20 years. (Courtesy the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion, 2000. http://www.cdc.gov/growthcharts.)
2 to 20 years: Girls
Stature-for-age and Weight-for-age percentiles

<table>
<thead>
<tr>
<th>NAME</th>
<th>RECORD #</th>
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</table>

**SOURCE:** Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

Published May 30, 2000 (modified 11/21/00).

Figure 13-1, cont'd
ill-advised regimens. Loss of control (binge) eating occurs among approximately 6% of children of this age.

Prior to puberty, the sensitivity of the hypothalamus and the pituitary changes, leading to increased gonadotropin synthesis. Interest in gender differences and sexual behavior increases progressively until puberty. Although this is a period when sexual drives are limited, masturbatory is common, and children may be interested in differences between genders. Sexual maturity occurs earlier for both genders in the United States. Rates of maturation differ by geography, ethnicity, and country. These differences in maturation have implications for differing expectations of others based on sexual maturation.

**Implications for Parents and Pediatricians**

Middle childhood is generally a time of excellent health. However, children have variable sizes, shapes, and abilities. Children of this age compare themselves with others, eliciting feelings about their physical attributes and abilities. Fears of being “abnormal” can lead to avoidance of situations in which physical differences might be revealed, such as gym class or medical examinations. Children with actual physical disabilities may face special stresses. Medical, social, and psychologic risks tend to occur together.

Children should be asked about risk factors for obesity. Participation in physical activity, including organized sports or other organized activities can foster skill, teamwork, and fitness, as well as a sense of accomplishment, but pressure to compete when the activity is no longer enjoyable has negative effects. Counseling on establishing healthy eating habits and limited screen time should be given to all families. Prepubertal children should not engage in high-stress, high-impact sports, such as power lifting or tackle football, because skeletal immaturity increases the risk of injury (see Chapter 693).

**COGNITIVE DEVELOPMENT**

The thinking of early elementary school-age children differs qualitatively from that of preschool children. In place of magical, egocentric, and perception-bound cognition, school-age children increasingly apply rules based on observable phenomena, factor in multiple dimensions and points of view, and interpret their perceptions using physical laws. Piaget documented this shift from preoperational to concrete logical operations. When 5 yr olds watch a ball of clay being rolled into a snake, they might insist that the snake has “more” because it is longer. In contrast, 7 yr olds typically reply that the ball and the snake must weigh the same because nothing has been added or taken away or because the snake is both longer and thinner. This cognitive reorganization occurs at different rates in different contexts. In the context of social interactions with siblings, young children often demonstrate an ability to understand alternate points of view long before they demonstrate that ability in their thinking about the physical world. Understanding time and space constructs occurs in the later part of this period.

The concept of “school readiness” has evolved. The American Academy of Pediatrics recommends following an “interactional relational” model in which the focus is on the child, the environment and the interactions therein. This model aid explicitly asserts that all children can learn and that the educational process is reciprocal between the child and the school. The model is developmentally based as it recognizes the importance of early experiences for later development. Rather than delaying school entry, high quality early education programs may be the key to ultimate school success.

School makes increasing cognitive demands on the child. Mastery of the elementary curriculum requires that a large number of perceptual, cognitive, and language processes work efficiently (Table 13-1), and children are expected to attend to many inputs at once. The 1st 2-3 yr of elementary school are devoted to acquiring the fundamentals: reading, writing, and basic mathematics skills. By 3rd grade, children need to be able to sustain attention through a 45 min period and the curriculum requires more complex tasks. The goal of reading a paragraph is no longer to decode the words, but to understand the content; the goal of writing is no longer spelling or penmanship, but composition. The volume of work increases along with the complexity.

Cognitive abilities interact with a wide array of attitudinal and emotional factors in determining classroom performance. These factors include external rewards (eagerness to please adults and approval from peers) and internal rewards (competitiveness, willingness to work for a delayed reward, belief in one’s abilities, and ability to risk trying when

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**Table 13-1**  Selected Perceptual, Cognitive, and Language Processes Required for Elementary School Success

<table>
<thead>
<tr>
<th>PROCESS</th>
<th>DESCRIPTION</th>
<th>ASSOCIATED PROBLEMS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PERCEPTUAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual analysis</td>
<td>Ability to break a complex figure into components and understand their spatial relationships</td>
<td>Persistent letter confusion (e.g., between b, d, and g); difficulty with basic reading and writing and limited “sight” vocabulary</td>
</tr>
<tr>
<td>Proprioception and motor control</td>
<td>Ability to obtain information about body position by feel and unconsciously program complex movements</td>
<td>Poor handwriting, requiring inordinate effort, often with overly tight pencil grasp; special difficulty with timed tasks</td>
</tr>
<tr>
<td>Phonologic processing</td>
<td>Ability to perceive differences between similar sounding words and to break down words into constituent sounds</td>
<td>Delayed receptive language skill; attention and behavior problems secondary to not understanding directions; delayed acquisition of letter-sound correlations (phonetics)</td>
</tr>
<tr>
<td><strong>COGNITIVE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term memory, both storage and recall</td>
<td>Ability to acquire skills that are “automatic” (i.e., accessible without conscious thought)</td>
<td>Delayed mastery of the alphabet (reading and writing letters); slow handwriting; inability to progress beyond basic mathematics</td>
</tr>
<tr>
<td>Selective attention</td>
<td>Ability to attend to important stimuli and ignore distractions</td>
<td>Difficulty following multistep instructions, completing assignments, and behaving well; problems with peer interaction</td>
</tr>
<tr>
<td>Sequencing</td>
<td>Ability to remember things in order; facility with time concepts</td>
<td>Difficulty organizing assignments, planning, spelling, and telling time</td>
</tr>
<tr>
<td><strong>LANGUAGE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Receptive language</td>
<td>Ability to comprehend complex constructions, function words (e.g., if, when, only, except), nuances of speech, and extended blocks of language (e.g., paragraphs)</td>
<td>Difficulty following directions; wandering attention during lessons and stories; problems with reading comprehension; problems with peer relationships</td>
</tr>
<tr>
<td>Expressive language</td>
<td>Ability to recall required words effortlessly (word finding), control meanings by varying position and word endings, and construct meaningful paragraphs and stories</td>
<td>Difficulty expressing feelings and using words for self-defense, with resulting frustration and physical acting out; struggling during “circle time” and in language-based subjects (e.g., English)</td>
</tr>
</tbody>
</table>
success is not ensured). Success predisposes to success, whereas failure impacts self-esteem and reduces self-efficacy, diminishing a child's ability to take future risks.

Children's intellectual activity extends beyond the classroom. Beginning in the 3rd or 4th grade, children increasingly enjoy strategy games and wordplay (puns and insults) that exercise their growing cognitive and linguistic mastery. Many become experts on subjects of their own choosing, such as sports trivia, or develop hobbies, such as special card collections. Others become avid readers or take on artistic pursuits. Whereas board and card games were once the usual leisure time activity of youth, video, computer and other electronic games currently fill this need.

**Implications for Parents and Pediatricians**

Pediatricians have an important role in preparing their patients for school entrance by promoting health through immunizations, adequate nutrition, appropriate recreation and screening for physical, developmental, and cognitive disorders. The American Academy of Pediatrics recommends that pediatric providers promote the “5 Rs” of early education: (1) reading as a daily family activity; (2) rhyming, playing, and cuddling together; (3) routines and regular times for meals, play, and sleep; (4) reward through praise for successes; and (5) reciprocal nurturing relationships.

Concrete operations allow children to understand simple explanations for illnesses and necessary treatments, although they may revert to prelogical thinking when under stress. A child with pneumonia may be able to explain about white cells fighting the “germs” in the lungs, but still secretly harbors the belief that the sickness is a punishment for disobedience.

As children are faced with more abstract concepts, academic and classroom behavior problems emerge and come to the pediatrician's attention. Referrals may be made to the school for remediation or to community resources (medical or psychologic) when appropriate. The causes may be one or more of the following: deficits in perception (vision and hearing); specific learning disabilities; global cognitive delay (mental retardation); primary attention deficit; and attention deficits secondary to family dysfunction, depression, anxiety, or chronic illness (see Chapters 16 and 32). Children whose learning style does not fit the classroom culture may have academic difficulties and need assessment before failure sets in. Simply having a child repeat a failed grade rarely has any beneficial effect and often seriously undercuts the child's self-esteem. In addition to finding the problem areas, identifying each child's strengths is important. Educational approaches that value a wide range of talents (“multiple intelligences”) beyond the traditional ones of reading, writing, and mathematics may allow more children to succeed.

The change in cognition allows the child to understand “if/when” clauses. Increased responsibilities and expectations accompany increased rights and privileges. Discipline strategies should move toward negotiation and a clear understanding of consequences, including removal of privileges for infringements.

**SOCIAL, EMOTIONAL, AND MORAL DEVELOPMENT**

**Social and Emotional Development**

In this period, energy is directed toward creativity and productivity. Changes occur in 3 spheres: the home, the school, and the neighborhood. Of these, the home and family remain the most influential. Increasing independence is marked by the first sleepover at a friend's house and the first time at overnight camp. Parents should make demands for effort in school and extracurricular activities, celebrate successes, and offer unconditional acceptance when failures occur. Regular chores, associated with an allowance, provide an opportunity for children to contribute to family functioning and learn the value of money. These responsibilities may be a testing ground for psychologic separation, leading to conflict. Siblings have critical roles as competitors, loyal supporters, and role models.

The beginning of school coincides with a child's further separation from the family and the increasing importance of teacher and peer relationships. Social groups tend to be same-sex, with frequent changing of membership, contributing to a child's growing social development and competence. Popularity, a central ingredient of self-esteem, may be won through possessions (having the latest electronic gadgets or the right clothes), as well as through personal attractiveness, accomplishments, and actual social skills. Children are aware of racial differences and are beginning to form opinions about racial groups that impact their relationships.

Some children conform readily to the peer norms and enjoy easy social success. Those who adopt individualistic styles or have visible differences may be teased. Such children may be painfully aware that they are different, or they may be puzzled by their lack of popularity. Children with deficits in social skills may go to extreme lengths to win acceptance, only to meet with repeated failure. Attributions conferred by peers, such as funny, stupid, bad, or fat, may become incorporated into a child's self-image and affect the child's personality, as well as school performance. Parents may have their greatest effect indirectly, through actions that change the peer group (moving to a new community or insisting on involvement in structured after-school activities).

In the neighborhood, real dangers, such as busy streets, bullies, and strangers, tax school-age children's common sense and resourcefulness. Interactions with peers without close adult supervision call on increasing conflict resolution or pugilistic skills. Media exposure to adult materialism, sexuality, substance use and violence may be frightening, reinforcing children's feeling of powerlessness in the larger world. Compensatory fantasies of being powerful may fuel the fascination with superheroes. A balance between fantasy and an appropriate ability to negotiate real-world challenges indicates healthy emotional development.

**Moral Development**

Although by age 6 yr most children will have a conscience (internalized rules of society), they vary greatly in their level of moral development. For the younger youth, many still subscribe to the notion that rules are established and enforced by an authority figure (parent or teacher) and decision-making is guided by self-interest (avoidance of negative and receipt of positive consequences). The needs of others are not strongly considered in decision-making. As they grow older, most will recognize not only their own needs and desires, but also those of others, although personal consequences are still the primary driver of behavior. Social behaviors that are socially undesirable are considered to be wrong. By age 10-11 yr the combination of peer pressure, a desire to please authority figures as well as an understanding of reciprocity (treat others as you wish to be treated) shapes the child's behavior.

**Implications for Parents and Pediatricians**

Children need unconditional support as well as realistic demands as they venture into a world that is often frightening. A daily query from parents over the dinner table or at bedtime about the good and bad things that happened during the child's day may uncover problems early. Parents may have difficulty allowing the child independence or may exert excessive pressure on their children to achieve academic or competitive success. Children who struggle to meet such expectations may have behavior problems or psychosomatic complaints.

Many children face stressors that exceed the normal challenges of separation and success in school and the neighborhood. Divorce affects nearly 50% of children. Domestic violence, parental substance abuse, and other mental health problems may also impair a child's ability to use home as a secure base for refueling emotional energies. In many neighborhoods, random violence makes the normal development of independence extremely dangerous. Older children may join gangs as a means of self-protection and a way to attain recognition and belong to a cohesive group. Children who bully others, and/or are victims of bullying, should be evaluated, since this behavior is associated with mood disorders, family problems, and school adjustment problems. Parents should reduce exposure to hazards where possible. Because of the risk of unintentional firearm injuries to children, parents should be encouraged to ask parents of playmates whether a gun is kept in
their home and, if so, how it is secured. The high prevalence of adjustment disorders among school-age children attests to the effects of such overwhelming stressors on development.

Pediatrician visits are infrequent in this period; therefore each visit is an opportunity to assess children's functioning in all contexts (home, school, neighborhood). Maladaptive behaviors, both internalizing and externalizing, occur when stress in any of these environments overwhelms the child's coping responses. Due to continuous exposure and the strong influence of media (programming and advertisements) on children's beliefs and attitudes, parents must be alert to exposures from the television and Internet. An average American youth spends over 6 hr/day with a variety of media, and ¾ of these children have a television in their bedrooms. Parents should be advised to remove the television from their children's rooms, limit viewing to 2 hr/day, and monitor what programs children watch. The Draw-a-Person (for ages 3-10 yr, with instructions to "draw a complete person") and Kinetic Family Drawing (beginning at age 5 yr, with instructions to "draw a picture of everyone in your family doing something") are useful office tools to assess a child's functioning.

Bibliography is available at Expert Consult.
Bibliography


Chapter 14

Adolescence

See Part XIII, Chapter 110, Adolescent Development.
Chapter 15
Assessment of Growth
Virginia A. Keane

Many biophysical and psychosocial problems can adversely affect growth, and aberrant growth may be the first sign of an underlying problem. The most powerful tool in growth assessment is the growth chart (see Figs. 11-1, 11-2, 13-1, and 15-1) used in combination with accurate measurements of height, weight, head circumference, and calculation of the body mass index (BMI).

PROcedures FOR Accurate MEASUREMENT
Growth assessment requires accurate measurement. Weight, in pounds or kilograms, must be determined using an accurate scale. For infants and toddlers, weight, length, and head circumference are obtained. These measures should be performed with the infant naked, and ideally, repeated measures should be performed on the same equipment. Head circumference is determined using a flexible tape measure run from the supraorbital ridge to the occiput in the path that leads to the largest possible measurement. Length is most accurately measured by 2 examiners (1 to position the child), with the child supine on a measuring board. For older children, the measure is stature or height, taken without shoes, using a stadiometer. Measurements obtained in alternative manners, such as marking examination paper at the foot and head of a supine infant, or using a simple wall growth chart with a book or ruler on the head can lead to inaccuracy that may render the measurement useless. It is essential to compare measurements with previous growth trends, repeat any that are inconsistent, and plot results longitudinally.

DERIVATION AND INTERPRETATION OF GROWTH CHARTS
In 2000, the Centers for Disease Control and Prevention (CDC) published new growth charts, replacing the 1977 version. Modifications since then have not changed the data points. Set 1 includes the 5th to 95th percentiles; set 2, the 3rd to 97th percentiles. These charts contain data from national surveys conducted by the National Center for Health Statistics between 1963 and 1994. Data are representative of the U.S. population, both demographically and in terms of breastfeeding prevalence. Methodologic steps have assured that the increase in the prevalence of obesity has not unduly raised the upper limits of normal. Several deficiencies of the older charts have been corrected, such as the over-representation of bottlefed infants and the reliance on a local data set for the infant charts. The disjunction between length and height, when moving from the infant curves to those for older children, no longer exists. The charts include curves for plotting BMI for ages 2-20 yr rather than weight for height, facilitating identification of obesity.

The data are presented in 5 standard gender-specific charts: (1) weight for age; (2) height (length and stature) for age; (3) head circumference for age; (4) weight for height (length and stature) for infants; and (5) BMI for age for children over 2 yr of age (see Fig. 15-1; also see Figs. 11-1, 11-2, and 13-1). The charts are available at http://www.cdc.gov/growthcharts/.

Each chart is composed of percentile curves, representing the cross-sectional distribution of weight, length, stature, head circumference, weight for length, or BMI at each age. The percentile curve indicates the percentage of children at a given age on the x-axis whose measured value falls below the corresponding value on the y-axis. On the weight chart for boys 0-36 mo of age (see Fig. 11-2A), the 90th percentile curve at 8.6 kg, indicating that 5% of the 9 mo old boys in the National Center for Health Statistics sample weigh less than 8.6 kg (75% weigh more). Similarly, a 9 mo old boy weighing more than 11.2 kg is heavier than 95% of his peers. The median or 50th percentile is also termed the standard value, in the sense that the standard height for a 7 mo old girl is 67 cm (see Fig. 11-2B). The weight-for-height charts (see Fig. 11-1) are constructed in an analogous fashion, with length or stature in place of age on the x-axis; the median or standard weight for a girl measuring 110 cm is 18.6 kg.

For infants, the revised CDC charts represent observed but not necessarily optimal growth because they still incorporate data from many bottlefed infants. Rates of initiation of breastfeeding in the United States have more than doubled from 26% in 1970 to 74% in 2005, but nationally only 49% continue to breastfeed at 6 mo, and only 27% continue until 12 mo. Compared with current standards, an exclusively breastfed infant would be expected to plot higher for weight in the 1st 6 mo, but relatively lower in the second half of the 1st yr. Awareness of this growth difference should prevent overidentification of growth problems in breastfed infants.

In an effort to set an internationally usable standard for optimal growth in children, the World Health Organization (WHO) released growth charts based on the Multicenter Growth Reference Study for young children in 2006 and for children 5-19 in 2007. Rather than describing the growth of typical children, the Multicenter Growth Reference Study describes the growth of children who are predominantly breastfed and raised under optimal conditions. Six study sites representing 5 continents were included: United States, Brazil, Norway, Ghana, Oman, and India. Use of the WHO charts in developing nations results in identification of many more children as malnourished and eligible for therapeutic feeding programs. Their use in the United States generally results in many fewer infants being identified as underweight (comparison of curves shown in Fig. 15-2), although studies have found overidentification of poor growth even using these curves. The CDC recommends the use of WHO charts for U.S. children from birth to 24 mo. Adoption of these charts in the United States has been slow. Charts are available online at http://www.who.int/childgrowth/standards/en/.
2 to 20 years: Boys
Body mass index-for-age percentiles

NAME ______________________  RECORD # __________

<table>
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*To Calculate BMI: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703

Figure 15-1 Body mass index (BMI) percentiles for boys (A) and girls (B) ages 2-20 yr. [Official Centers for Disease Control (CDC) growth charts, as described in this chapter. The 85th to 95th percentile is at risk for overweight; >95th percentile is overweight; <5th percentile is underweight. Technical information and interpretation and management guides are available at www.cdc.gov/nchs. Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion, 2000. http://www.cdc.gov/growthcharts)
2 to 20 years: Girls
Body mass index-for-age percentiles

*To Calculate BMI: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703

Published May 30, 2000 (modified 10/16/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with
the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

Figure 15-1, cont’d
Assessment

3.5 2.00 115
1.0 0.25 100

Growth and Caloric Requirements

90-100
87
3
6
2.0 1.00 110
15
8
20
1.25
30
8
1.2 0.50 100
6
12
1.5 0.50 100
2
5


For adolescents, caution must be used in applying cross-sectional charts. Growth during adolescence is linked temporally to the onset of puberty, which varies widely. By using cross-sectional data based on chronological age, the charts combine youth who are at different stages of maturation. Normal variations in the timing of the growth spurt can lead to misdiagnosis of growth abnormalities. The data for 12 yr old boys include both early-maturing boys who are at the peak of their growth spurts and late-maturing ones who are still growing at their prepubertal rate. The net result is to artificially level off the growth peak, making it appear that adolescents grow more gradually and for a longer period than they do. When additional precision is necessary, growth charts derived from longitudinal data, such as the height velocity charts of Tanner and colleagues, are recommended.

Specialized charts have been developed for U.S. children with various conditions, including very-low birthweight and prematurity; Down, Turner, and Klinefelter syndromes; cerebral palsy; and achondroplasia. In addition, growth charts for children of distinct ethnic groups or nationalities may be found on the World Wide Web.

BMI for age complements the standard growth charts for children older than 2 yr of age. BMI can be calculated as weight in kilograms/ (height in meters)² or weight in pounds/(height in inches)² × 703, with fractions of pounds and inches expressed as decimals. Values may be plotted on standard BMI charts (see Fig. 15-1). These calculations can be easily performed electronically using a variety of desktop and handheld devices. BMI percentile varies with age over childhood: a 6 yr old girl with a BMI of 21 is overweight, whereas a 16 yr old girl with the same BMI is just above the 50th percentile.

Electronic medical records (EMRs) include growth charts and usually calculate and plot BMIs. However, the origin of the growth charts that are included in the EMRs used by a pediatrician may be unknown to the pediatrician; consequently, pediatricians are cautioned to contact their EMR company and assure that the CDC and WHO growth charts are available in the EMRs to assure accurate assessment.

Height velocity charts, which evaluate the rate of growth per year, are considered by many to give a more sensitive and specific indicator of abnormal growth. They are used primarily by pediatric endocrinologists. Although many parents think it is important to see growth charts, parents may misinterpret their meaning. Clinicians are cautioned to provide clear interpretation when using growth charts as visual aids.

ANALYSIS OF GROWTH PATTERNS

Growth is a process rather than a static quality. An infant at the 5th percentile of weight for age may be growing normally, may be failing to grow, or may be recovering from growth failure, depending on the trajectory of the growth curve. Infants may lose up to 10% of their birth weight in the 1st wk of life and regain it by the end of the 2nd wk. They will then gain steadily at a rate of 20-30 g/day for the 1st 3 mo. Table 15-1 gives typical growth and calorie requirements for children through age 6 yr. Formulas are available for the estimation of average height

![Figure 15-2](image-url) Comparison of the WHO and CDC growth chart prevalences of low length for age, low weight for age, and high weight for age among children ages younger than 24 months—United States, 1999-2004. * ≤5th percentile on the CDC charts; ≥2.3rd percentile on the WHO charts. † ≥95th percentile on the CDC charts; ≥97.7th percentile on the WHO charts. (Data from the National Health and Nutrition Examination Survey, 1999-2004; from Grummer-Strawn LM, Reinold C, Krebs NF, Centers for Disease Control and Prevention, Use of World Health Organization and CDC growth charts for children aged 0-59 months in the United States. MMWR Recomm Rep 59 (RR-9):1-15, 2010, Fig. 6.)
and weight and height for children of various ages, but given their complexity and the easy availability of growth charts, use of the latter is preferable.

Despite the facts that the National Center for Health Statistics charts represent cross-sectional rather than longitudinal data and that children tend to grow in spurts, most children tend to track along a percentile, referred to as following the curve. A normal exception commonly occurs between 6 and 18 mo of life. For full-term infants, size at birth reflects the influence of the uterine environment; however, size at 2 yr correlates with mean parental height, reflecting the influence of genes. Between 6 and 18 mo of age, infants may shift percentiles upward or downward toward their genetic potential. Thereafter, most children will track along a growth percentile, with variation within 2 large percentile bands (a small infant might track between the 5th and 25th percentiles, a large one between the 75th and 95th). This tracking often represents the midparental height and a corresponding weight, where midparental height is calculated in inches as follows:

- Boys: \[(\text{maternal height} + 5) + \text{paternal height}/2\]
- Girls: \[(\text{maternal height} + \text{paternal height} − 5)/2\]
- 13 cm (instead of \(\pm 5\) in) if using metric units

It is important to correct for various factors in plotting and interpreting growth charts. For premature infants, overdiagnosis of growth failure can be avoided by using growth charts developed specifically for this population. A cruder method, subtracting the weeks of prematurity from the postnatal age when plotting growth parameters, does not capture the variability in growth velocity that very-low-birthweight infants demonstrate. Although very-low-birthweight infants may continue to show catchup growth through early school age, most achieve weight catchup during the 2nd yr and height catchup by 2.5 yr, barring medical complications (see Chapter 97). For children with particularly tall or short parents, there is a risk of overdiagnosing growth disorders if parental height is not taken into account or, conversely, of underdiagnosing growth disorders if parental height is accepted uncritically as the explanation.

The analysis of growth patterns and the detection of aberrant growth patterns provide critical information for the detection of pathologic conditions. Calculation of daily and monthly growth, such as weight gain in g/yr (see Table 15-1), allows more precise comparison of growth rate to the norm. Weight loss, or failure to gain normally, is often the first sign of pathology.

The diagnosis of failure to thrive (see Chapter 41), usually a diagnosis of children younger than 3 yr of age, is considered if a child's weight is below the 5th percentile, if it drops more than 2 major percentile lines, or if weight for height is less than the 5th percentile. Weight for height below the 5th percentile remains the single best indicator of undernutrition. A BMI less than the 5th percentile also indicates that a child is underweight. Brief periods of weight loss or poor weight gain are usually rapidly corrected and do not permanently affect size. Children who have been chronically malnourished may be short (stunted) as well as thin, so that their weight-for-height curves may appear relatively normal. Chronic, severe undernutrition in infancy may depress head growth, which may be an ominous predictor of later cognitive disability. Low weight for age or height or weight loss may be referred to as wasting. When growth parameters fall below the 5th percentile, values can be expressed as percentages of the median, or standard, value. A 12 mo old girl weighing 7.1 kg is at 75% of the median weight (9.5 kg) for her age.

Another way to evaluate weight is to determine the ideal body weight for height and compare the current weight to the ideal body weight for length or height. A 15 mo old boy who is 79 cm is at the 50th percentile. The ideal weight is 12 kg. If he weighs 8 kg (<5th percentile), he is 67% of ideal body weight, an indication of severe wasting. Table 15-2 provides interpretation of percent ideal body weight from obese to severe wasting.

Extremes of height or weight can also be expressed in terms of the age for which they would represent the standard or median. For instance, a 30 mo old girl who is 79 cm (<5%) is at the 50th percentile for a 16 mo old. Thus the height age is 16 mo. Weight age can also be expressed this way.

### Table 15-2  Interpretation of Percent of Ideal Body Weight

<table>
<thead>
<tr>
<th>Percent</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>&gt;120%</td>
<td>Obese</td>
</tr>
<tr>
<td>110-120%</td>
<td>Overweight</td>
</tr>
<tr>
<td>90-110%</td>
<td>Normal variation</td>
</tr>
<tr>
<td>80-90%</td>
<td>Mild wasting</td>
</tr>
<tr>
<td>70-80%</td>
<td>Moderate wasting</td>
</tr>
<tr>
<td>&lt;70%</td>
<td>Severe wasting</td>
</tr>
</tbody>
</table>

Linear growth deficiency (stunting) is more likely to be a result of congenital, constitutional, familial, or endocrine causes than caused by nutritional deficiency (see Chapter 46). In endocrine disorders, length or height declines first or at the same time as weight; weight for height is normal or elevated. In nutritional insufficiency, weight declines before length, and weight for height is low (unless there has been chronic stunting). Figure 15-3 depicts typical growth curves for 4 classes of decreased linear growth. In congenital pathologic short stature, an infant is born small and growth gradually tapers off throughout infancy. Causes include chromosomal abnormalities (Turner syndrome, trisomy 21; see Chapter 81), perinatal infection, extreme prematurity, and teratogens (phenytoin, alcohol) (see Chapter 96). In constitutional growth delay, weight and height decrease near the end of infancy, parallel the norm through middle childhood, and accelerate toward the end of adolescence. Adult size is normal. In familial short stature, both the infant and the parents are small; growth runs parallel to and just below the normal curves.

Obesity affects large numbers of children. Growth charts can confirm an impression of obesity if the weight for height exceeds 120% of the standard (median) weight for height. According to the CDC, a BMI over the 95th percentile indicates obesity and a BMI between the 85th and 95th percentiles indicates overweight. Although widely accepted as the best clinical measure of under- and overweight, BMI may not provide an accurate index of adiposity, because it does not differentiate lean tissue and bone from fat. Measurement of the triceps, subscapular, and suprailiac skinfold thickness can be used to estimate adiposity; considerable experience is needed for accuracy. The American Academy of Pediatrics Nutrition Handbook, 6th edition, questions the use of fat folds to estimate total body fat, noting that the method has not been validated in young children and that basic assumptions of the method, that subcutaneous fat is a marker of total fat and that measured sites represent average skin fat thickness, are not true. Other methods of measuring fat, such as hydrodensitometry, bioelectrical impedance, and total body water measurement are used in research, but not in clinical evaluation.

### OTHER INDICES OF GROWTH

#### Body Proportions

Body proportions follow a predictable sequence of changes with development. The head and trunk are relatively large at birth, with progressive lengthening of the limbs throughout development, particularly during puberty. The **lower-body segment** is defined as the length from the symphysis pubis to the floor, and the **upper-body segment** is the height minus the lower-body segment. The ratio of upper-body segment divided by lower-body segment (U/L ratio) equals approximately 1.7 at birth, 1.3 at 3 yr of age, and 1.0 after 7 yr of age. Higher U/L ratios are characteristic of short-limb dwarfism or bone disorders, such as rickets.

#### Skeletal Maturation

Reference standards for bone maturation facilitate estimation of bone age (see Table 10-3). Bone age correlates well with stage of pubertal development and can be helpful in predicting adult height in early- or late-maturing adolescents. In familial short stature, the bone age is normal (comparable to chronological age). In constitutional delay,
immediately or may lag by 4-5 mo. The timing of dental development is poorly correlated with other processes of growth and maturation. 

Delayed eruption is usually considered when there are no teeth by approximately 13 mo of age (mean + 3 SD). Common causes include hypothyroid, hypoparathyroid, familial, and (the most common) idiopathic. Individual teeth may fail to erupt because of mechanical blockage (crowding, gum fibrosis). Causes of early exfoliation include histiocytosis X, cyclic neutropenia, leukemia, trauma, and idiopathic factors. Nutritional and metabolic disturbances, prolonged illness, and certain medications (tetracycline) commonly result in discoloration or malformations of the dental enamel. A discrete line of pitting on the enamel suggests a time-limited insult.

Bibliography is available at Expert Consult.

**Table 15-3** Chronology of Human Dentition of Primary or Deciduous and Secondary or Permanent Teeth

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<th>Age at Shedding</th>
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<td>Maxillary</td>
<td>Mandibular</td>
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<tr>
<td>Central incisors</td>
<td>5th fetal mo</td>
<td>6-8 mo</td>
<td>7-8 yr</td>
</tr>
<tr>
<td>Lateral incisors</td>
<td>5th fetal mo</td>
<td>8-11 mo</td>
<td>8-9 yr</td>
</tr>
<tr>
<td>Cuspids (canines)</td>
<td>6th fetal mo</td>
<td>16-20 mo</td>
<td>11-12 yr</td>
</tr>
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<td>First molars</td>
<td>5th fetal mo</td>
<td>10-16 mo</td>
<td>10-12 yr</td>
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<td>Second molars</td>
<td>6th fetal mo</td>
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<td><strong>SECONDARY TEETH</strong></td>
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<td>Mandibular</td>
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<td>7-8 yr</td>
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<td>9-11 yr</td>
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<td>6-7 yr</td>
</tr>
<tr>
<td>Second molars</td>
<td>30-36 mo</td>
<td>12-13 yr</td>
<td>12-13 yr</td>
</tr>
<tr>
<td>Third molars</td>
<td>Max, 7-9 yr</td>
<td>17-22 yr</td>
<td>17-22 yr</td>
</tr>
</tbody>
</table>

Mand, Mandibular; Max, maxillary.

Adapted from a chart prepared by P.K. Losch, Harvard School of Dental Medicine, who provided the data for this table.

endocrinologic short stature, and undernutrition, the bone age is low and comparable to the height age. Skeletal maturation is linked more closely to sexual maturity rating than to chronological age. It is more rapid and less variable in girls than in boys.

**Dental Development**

Dental development includes mineralization, eruption, and exfoliation (Table 15-3). Initial mineralization begins as early as the 2nd trimester (mean age for central incisors, 14 wk) and continues through 3 yr of age for the primary (deciduous) teeth and 25 yr of age for the permanent teeth. Mineralization begins at the crown and progresses toward the root. Eruption begins with the central incisors and progresses laterally. Exfoliation begins at about 6 yr of age and continues through 12 yr of age. Eruption of the permanent teeth may follow exfoliation immediately or may lag by 4-5 mo. The timing of dental development is poorly correlated with other processes of growth and maturation. 

Delayed eruption is usually considered when there are no teeth by approximately 13 mo of age (mean + 3 SD). Common causes include hypothyroid, hypoparathyroid, familial, and (the most common) idiopathic. Individual teeth may fail to erupt because of mechanical blockage (crowding, gum fibrosis). Causes of early exfoliation include histiocytosis X, cyclic neutropenia, leukemia, trauma, and idiopathic factors. Nutritional and metabolic disturbances, prolonged illness, and certain medications (tetracycline) commonly result in discoloration or malformations of the dental enamel. A discrete line of pitting on the enamel suggests a time-limited insult.

Bibliography is available at Expert Consult.
Bibliography
Centers for Disease Control and Prevention, National Center for Health Statistics: *CDC growth charts (website)*, http://www.cdc.gov/growthcharts/.
The term developmental–behavioral refers to children's language, motor, cognitive/academic, self-help, and social–emotional status (a term that also embraces conduct, mental health, attention, and well-being). At well-child visits, development and behavior are the most common topic in parent–professional discussions. Early developmental–behavior problems are common (20-25%) but not benign. Left untreated, early deficits often burgeon into school failure and secondary mental health problems. The consequences include leaving high school before graduating (with rates in inner cities and among minority youth ranging as high as 50%), unemployment, incarceration, and teen pregnancy.

To prevent and address problems, clinicians must screen for existing limitations and risks.

MEASURABLE DELAYS
Among the many types of developmental–behavioral conditions, language problems are the most common (17.5% at 30-36 mo) (see Chapter 35). Delays in language development are often overlooked by healthcare providers, particularly when accurate screening/surveillance tools are not used. Other common conditions are social–emotional/behavioral/mental health disorders (9.5-14.2%), attention-deficit/hyperactivity disorder (7.8%) (see Chapter 33), learning disabilities (6.5%), intellectual disabilities (1.2%) (see Chapter 36), and autism spectrum disorders (0.6-1.1%) (see Chapter 30). Less common conditions include cerebral palsy and other orthopedic/motor impairments (0.23%) (see Chapter 598.1), hearing impairment (0.12%) (see Chapters 636-643), vision impairment (0.8%) (see Chapters 618-635), and conditions associated with disabilities (e.g., Down syndrome and fragile X syndrome [see Chapter 81], traumatic brain injury [see Chapter 68]).

PSYCHOSOCIAL RISK
Many children at risk for school failure lack measurable deficits in early childhood but have markers in the form of multiple risk factors that are strong predictors of future problems. Psychosocial risks include parents with less than a high school education; parental mental health problems such as depression or anxiety; housing or food instability; ethnic or linguistic minority; single parent; or more children in the home; and parenting styles that are neglectful or authoritarian (e.g., highly directive, punitive, limited verbal communication such as talking about children's interests or book-sharing). Such risks eventually lead to developmental–behavioral delays, and result in children entering kindergarten behind their peers, being held back in grade, dropping out of high school, etc. Although psychosocial risk factors are common in children with a history of abuse or neglect, children in many other families are also at-risk.

EARLY INTERVENTION SERVICES AND ELIGIBILITY CRITERIA
If intervention is instituted prior to school entrance, many problems can be prevented and all can be ameliorated. Early intervention takes many forms, requiring varying degrees of intensity.

Developmental–behavioral promotion in primary care is one form of intervention and recommended at all visits. Clinicians identify

and intervene with difficulties (e.g., with parent–child interactions and children's behavior), address parents' concerns and provide guidance on child-rearing and other issues. Role-playing, coaching, and verbal advice coupled with take-home information handouts are optimal approaches, although follow-up is needed to determine whether parents capitalized on directives or whether more intensive parent education is needed (e.g., parenting classes). Early intervention in primary care also involves identifying delays, risk factors for future delays, and referring for services more intensive than brief in-office counseling:

For children with psychosocial risk factors but without measurable delays, referrals are needed to a range of services such as Head Start/Early Head Start or quality daycare programs. Families often benefit from parent training classes or mental health interventions and referrals to social work services (e.g., for housing and food assistance, help with domestic violence). Older children with risk factors, benefit from dropout prevention assistance, including after-school tutoring, Boys and Girls Club, summer school, and mentoring programs.

For children with measurable delays (and those at extreme risk such as children in foster care) referrals are needed to services funded by the Individuals with Disabilities Education Act (IDEA). Very young children with delays, (i.e., birth to 3 yr of age) are eligible under the broad category of "developmental delay," defined as a single 40% departure or two 25% departures from typical performance in various developmental domains (e.g., receptive language, expressive language, fine motor, gross motor, social–emotional, cognitive/academic, and behavior). Because screening measures identify probable strengths and weaknesses but not the extent of deficits, clinicians should refer to IDEA programs for free evaluations to determine eligibility. When children are 3 yr of age, IDEA programs (administered by the public schools) provide detailed evaluations leading to definitive diagnoses and to a range of special education services and adjunctive therapies.

PRIMARY CARE CHALLENGES IN EARLY DETECTION
Despite the serious long-term consequences of psychosocial risk factors, delays and disabilities, only approximately 30% of children with developmental–behavioral problems are detected by primary care providers prior to school entrance, which means that most children with problems miss opportunities for early intervention. There are several reasons for underdetection in primary care:

- **Overconfidence in the effectiveness of informal identification methods** (e.g., ad-hoc questions to parents and milestones checklists such as those embedded in age-specific encounter forms, even if items are drawn from lengthier standardized measures such as the Denver Developmental Screening Test). Informal approaches are of little benefit to patients (or clinicians) because they lack validity, proof of accuracy, and definitive criteria for making referral decisions;

- **Overdependence on clinical judgment and failure to scrutinize the seemingly asymptomatic.** Dysmorphology and organicity are not present in the majority of children with disabilities;

- **Overfocusing on symptoms and thus missing underlying issues.** For example, behavior problems are often the presenting complaint, but many children with developmental deficits act out in frustration due to difficulties understanding what is being asked or expressing thoughts, desires, and feelings in words;

- **Lack of familiarity with and deployment of accurate screening tools effective for busy primary care settings;**

- **An erroneous sense that quality measures take more time than informal approaches;**

- **Excessive optimism about the effectiveness of brief in-office advice when children have measured delays,** and thus deferring rather than referring. Children rarely outgrow developmental–behavioral problems in the absence of intervention;

- **Discomfort at delivering difficult news.** Clinicians require skill at conducting interviews in which difficult news is delivered in a manner that is supportive, positive, and impels families to follow through with recommendations.
POLICIES OF THE AMERICAN ACADEMY OF PEDIATRICS

The American Academy of Pediatrics (AAP) recommends a combination of screening and surveillance at all well-visits.

**Screening** refers to the administration of brief, standardized, and validated instruments shown to have high sensitivity in detecting children with probable problems and high specificity in determining when children probably do not have problems. Screening for delays should occur across all domains: language (expressive and receptive), motor (gross and fine), cognitive/academic (including features of autism spectrum disorder), self-help, and social–emotional (including conduct, attention, and mental health).

Repeated screening compensates for underdetection. Developmental–behavioral problems are a “moving target” and thus require ongoing measurement. Although AAP policies identify specific ages when formal screening should occur (e.g., 9-, 18-, 24- or 30-mo), clinicians should not interpret AAP recommendations to mean that screening/surveillance can cease after 30 mo. Problems (such as language or school readiness) may still be emerging and will not be fully manifested in very young children. The AAP policy states that screening/surveillance should be provided at all well visits and is actively advocating for payers to reimburse for identification efforts with older children.

Although clinicians are often concerned about overidentification, most children with false-positive screens, although ineligible for special education services, have moderate delays in areas predictive of future school failure, that is, language, intelligence, and academic/preadolescent skills, along with elevated psychosocial risk. Such children are in need of referrals to other types of intervention programs (e.g., Head Start, after-school tutoring, summer school, and quality preschool or daycare).

Use of accurate screens provides a focus for other well-visit activities. For example, screens relying on parents’ concerns identify specific topics for developmental–behavioral promotion. The presence of delays prompts clinicians to conduct a particularly careful physical exam; repeat hearing and vision screening; thoughtfully observe parent–child interactions; take an especially detailed family medical/social history; and similar actions.

Deployment of quality screens provides decision support for the types of interventions needed, including whether clinical advice is sufficient, whether more intensive hands-on services are required, and/or subspecialty medical referrals are needed.

**Surveillance** refers to ongoing monitoring (tracking over time) of such issues as parental concerns, children’s progress with milestones, psychosocial risk and resilience factors, providers’ efforts to both detect and address problems, and follow-up regarding child/family outcomes. Surveillance also refers to use of clinical acumen in decision making via the incorporation of screening test results, child/family medical histories, and the physical exam. Repeated accurate screening also serves the tasks of surveillance, but with efficiency and effectiveness. Informal approaches to surveillance are known to be ineffective and of little benefit to families.

OVERCOMING LOGISTICAL CHALLENGES IN PRIMARY CARE EARLY DETECTION AND INTERVENTION

The lists of potential developmental–behavioral topics to be covered at well-child visits are extensive—far more than could be covered in the 14-18 min allotted for such encounters. It is essential to cull topics to those of greatest interest to parents so as to create “the teachable moment” wherein parents are primed to learn most from clinicians’ recommendations. Solutions include posters in waiting rooms listing the range of topics on which providers can advise; previsit checklists on which parents indicate topics of interest (and which topics have already been covered in prior visits); and use of use quality screening tests eliciting parents’ specific concerns and providing decision support, that is, when advice is probably sufficient vs when referrals are needed.

Clinicians are not always aware of the plethora of services available to families. Approaches to overcome this problem include creating a list of community programs to post in each exam room so that options are visible to parents and providers and encouraging non-medical services to provide prompt feedback on the status of referrals (e.g., establishing two-way consent forms for information sharing), evaluation results and recommendations. Implementing quality screens and patient education in practices requires thoughtful planning and generating enthusiasm among clinic staff who must aid in the process. Clinic flow templates and implementation worksheets are useful tools for establishing efficient implementation procedures.

Evidence-Based Tools

Table 16-1 shows a range of measures useful for early detection of psychosocial risk and resilience, and developmental–behavioral problems, including autism spectrum disorders. Because well-child visits are brief and have enormous agendas (physical exams, immunizations, anticipatory guidance, safety and injury prevention, developmental promotion, and development–behavioral screening/surveillance), tools relying on information from parents are ideal because they can be completed in advance of appointments, either online or in writing, whether at home, or while waiting for the encounter to begin. If tools are scored in advance of the patient encounter, clinicians can enter the exam room armed with needed information (e.g., parenting handouts, descriptions of services).

A Workable Process: Step-By-Step

The process of surveillance/screening as drawn from AAP policies is depicted in Figure 16-1 with a description provided in Table 16-2. Many tasks are staggered across visits so that each visit is only minimally burdened with measurement. Red flags are noted in Table 16-3 but are not a substitute for evidence-based screening. Asymptomatic children are those most in need of screening. Those with obvious symptoms simply need referral.

Table 16-2 mentions a range of tools by abbreviations as denoted Table 16-1. The Resources Section (Table 16-4) provides guidance on finding supportive information, practice tools, and the like.

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**Figure 16-1 Developmental-behavioral surveillance/screening at well-visits with children from birth to 6 yr of age: step-by-step.**

**Table 16-1. The Resources Section (Table 16-4) provides guidance on finding supportive information, practice tools, and the like.**

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**Bibilography is available at Expert Consult.**

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**Table 16-1**

<table>
<thead>
<tr>
<th>Task</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elicit parents’ concerns</td>
<td>A.</td>
</tr>
<tr>
<td>Measure children’s skills</td>
<td>B.</td>
</tr>
<tr>
<td>Identify/update psychosocial risk factors</td>
<td>C.</td>
</tr>
<tr>
<td>Observe/measure parent-child interactions and resilience factors</td>
<td>D.</td>
</tr>
<tr>
<td>Identify/update family and child medical history and biological risk factors</td>
<td>E.</td>
</tr>
<tr>
<td>Conduct a careful physical exam</td>
<td>F.</td>
</tr>
<tr>
<td>Provide developmental and behavioral promotion</td>
<td>G.</td>
</tr>
<tr>
<td>Interpret results, explain findings, decide on any needed referrals</td>
<td>H.</td>
</tr>
<tr>
<td>Document current findings, make needed referrals</td>
<td>I.</td>
</tr>
<tr>
<td>Ensure a medical home</td>
<td>J.</td>
</tr>
</tbody>
</table>

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**Table 16-2**

<table>
<thead>
<tr>
<th>Task</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen milestones in all domains</td>
<td>1.</td>
</tr>
<tr>
<td>Autism specific screening at 18 and 24 months</td>
<td>2.</td>
</tr>
<tr>
<td>Conduct a careful physical exam</td>
<td>3.</td>
</tr>
<tr>
<td>Provide developmental and behavioral promotion</td>
<td>4.</td>
</tr>
<tr>
<td>Interpret results, explain findings, decide on any needed referrals</td>
<td>5.</td>
</tr>
<tr>
<td>Document current findings, make needed referrals</td>
<td>6.</td>
</tr>
<tr>
<td>Ensure a medical home</td>
<td>7.</td>
</tr>
</tbody>
</table>

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**Table 16-3**

<table>
<thead>
<tr>
<th>Task</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen milestones in all domains</td>
<td>1.</td>
</tr>
<tr>
<td>Autism specific screening at 18 and 24 months</td>
<td>2.</td>
</tr>
<tr>
<td>Provide developmental and behavioral promotion</td>
<td>3.</td>
</tr>
<tr>
<td>Interpret results, explain findings, decide on any needed referrals</td>
<td>4.</td>
</tr>
<tr>
<td>Document current findings, make needed referrals</td>
<td>5.</td>
</tr>
<tr>
<td>Ensure a medical home</td>
<td>6.</td>
</tr>
</tbody>
</table>
The following chart is a list of measures meeting standards for screening test accuracy, meaning that they correctly identify, at all ages, at least 70-80% of children with disabilities while also correctly identifying at least 70-80% of children without disabilities. All listed measures were standardized on national samples, proven to be reliable, and validated against a range of diagnostic measures and diagnosed conditions. Not included are measures that fail to meet psychometric standards (limited standardization, absent validation, problematic sensitivity and specificity) such as Denver-II.

The first column provides publication information and the cost of purchasing a specimen set. The “Purpose and Description” column provides details about content and information on alternative ways, if available, to administer measures (e.g., waiting rooms). “Scoring” shows the types of results rendered. The “Accuracy” column shows the percentage of patients with and without problems identified correctly. The “Time Frame/Costs” column shows the costs of materials per visit, along with the costs of professional time (using an average salary of $60/hr) needed to administer each measure, but does not include time needed for generating referral letters. For parent self-report tools, administration time reflects not only scoring of test results, but also the relationship between each test’s reading level and the percentage of parents with less than a high school education (who may or may not be able to complete measures in waiting rooms because of literacy problems and thus will need interview administrations).

### Screens for Primary Care

#### Behavioral and/or Developmental Screens Relying on Information From Parents

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Purpose and Description</th>
<th>Scoring</th>
<th>Accuracy</th>
<th>Time Frame/Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-66 mo</td>
<td>Purpose: Screening and surveillance of developmental milestones Description: Parents indicate children’s developmental skills on 30 items plus overall concerns. The ASQ has a different form (5-8 pages) for each age interval. Written at the 4th-6th grade level. Can be used in mass mail-outs for child-find programs. Manual contains detailed instructions for organizing child-fnd programs and includes activity handouts for parents. The ASQ-3 is available in English and Spanish; the ASQ-2 is also available in French and Korean with additional translations underway. The ASQ-3 Learning Activities Kit is helpful for developmental promotion Cutoff scores set at 2 SD below the mean, in 5 developmental domains; indicate need for referral or monitoring By age: Sensitivity: 82.89% Specificity: 77.92% By domain: Sensitivity: 83% Specificity: 91% By disabilities: i.e., cerebral palsy, visual and hearing impairment: Sensitivity: 87%</td>
<td>Scoring time: 2 min Scoring cost: $2.40 Materials: $0.36-$0.48 Total Self-Report: $2.76-$2.88 Interview Time: 12 min. Interview Cost: $14.40 Scoring/Materials: $2.76-$2.88 Total Interview: $17.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth-8 yr</td>
<td>Purpose: Screening/surveillance of development/social-emotional/behavior/mental health via parents’ concerns Description: 10 questions eliciting parents’ (and providers’) concerns in English, Spanish, Vietnamese and many other languages. Items written at the 5th grade level. Longitudinal Score and Interpretation Forms, assign risk levels, track decision making and offer specific guidance on how to address concerns. Provides screening, longitudinal surveillance, and triage for both developmental and behavioral/social-emotional/mental health problems. PEDS can be used in conjunction with the PEDS-DM (below) for compliance with AAP policies on screening and surveillance, i.e., eliciting and addressing parents’ concerns and monitoring milestones Identifies when to refer and what types of referrals are needed; advise parents; monitor vigilantly; screen further (or refer for screening); or reassure By age: Sensitivity: 91.97% Specificity: 73-86% By disabilities, i.e., learning, intellectual, language, mental health, and autism spectrum disorders: Sensitivity: 71-87%</td>
<td>Scoring time: 1 min Scoring cost: $1.20 Materials: $0.39 Total Self-Report: $1.59 Interview Time: 2 min Interview Cost: $2.40 Scoring/Materials: $1.59 Total Interview: $3.99</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Table 16-1** Print and Online Tools for Developmental–Behavioral Screening and Surveillance

| Ages & Stages Questionnaires, Third Edition (ASQ-3) (2009) | Purpose: Identifies when to refer and what types of referrals are needed; advise parents; monitor vigilantly; screen further (or refer for screening); or reassure | Sensitivity: 82-89% Specificity: 77-92% |
| Training Options: Electronic Options: See below | Materials: ~$0.36-$0.48 | Cost: $0.36-$0.48 |

| Parents' Evaluations of Developmental Status (PEDS) (2013) PEDSTest.com | Purpose: Identifies when to refer and what types of referrals are needed; advise parents; monitor vigilantly; screen further (or refer for screening); or reassure | Sensitivity: 82-89% Specificity: 77-92% |
| Training Options: Offers through its website self-training/train-the-trainer support via downloadable slide shows with notes, case examples, and live training | Materials: ~$0.36-$0.48 | Cost: $0.36-$0.48 |
**Pediatric Evaluation of Developmental Status (PEDS)**

**Purpose:** Screening/surveillance of developmental and social-emotional/mental health milestones.

**Description:** PEDS-DM is designed to replace informal milestones checklists (such as items from other measures) with evidence. It consists of 6-8 items at each age level. Each item taps a different domain: fine/gross motor, self-help, academics, expressive/receptive language, social-emotional. The PEDS: DM provides screening, triage, and surveillance via a longitudinal score form for tracking developmental milestones progress. Written at the 2nd-3rd grade level and can be completed by self-report, interview, or administered directly to children. Forms are laminated and completed with a dry erase marker. Supplemental measures focused on AAP policy include the M-CHAT, Family Psychosocial Screen, Pictorial PSC-17, the SWILS, the Vanderbilt ADHD scale, and the Brigance Parent-Child Interactions Scale. When combined with PEDS, ensures full compliance with AAP policy. In English, Spanish, Taiwanese, and Portuguese, with other languages in process. The PEDS: DM manual and website contain developmental-behavioral promotion handouts.

**Training Options:** Offers through its website self-training/train-the-trainer support via downloadable slide shows with notes, case examples, pre-/posttest questions, participant handouts, FAQs, website discussion list (covering all screens), short videos, with some live training available. The PEDS: DM manual includes extensive suggestions for training medical students, residents, and nurses.

**Electronic Options:** See below

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**Narrowband Screens Relying on Information from Parents**

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Purpose</th>
<th>Purpose and Description</th>
<th>Scoring</th>
<th>Accuracy</th>
<th>Time Frame/Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth-8 yr</td>
<td>Screening for developmental and social-emotional/mental health milestones</td>
<td>Pass/fail cutoffs tied to performance above and below the 16th percentile for each item and its domain</td>
<td>By age: Sensitivity: 70-94%; Specificity: 77-93%</td>
<td>Scoring Time: 1 min</td>
<td>Total Direct Admin: $6.10</td>
</tr>
</tbody>
</table>

**Parent-report narrow-band screens** (for social-emotional/behavioral/mental health, psychosocial risk, and autism spectrum disorder). These are valuable adjuncts in primary care and in other settings but only when preceded by a broadband screen. Narrowband tools should not be used as the sole measure of developmental-behavioral status.

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**Modified Checklist for Autism in Toddlers (M-CHAT) (1999).** Freely downloadable in multiple languages along with the follow-up Interview at [www.mchatscreen.com](http://www.mchatscreen.com). Also included in print in PEDS: Developmental Milestones. Commercial software vendors must pay a licensing fee.

**Training Options:** The site contains a guide to the needed follow-up interview for missed items, and houses research papers and reviews on autism spectrum disorder (ASD) screening.

**Electronic options:** See below

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**Chapter 16 Developmental-Behavioral Screening and Surveillance**
### Table 16-1 | Print and Online Tools for Developmental–Behavioral Screening and Surveillance—cont’d

<table>
<thead>
<tr>
<th>NARROWBAND SCREENS RELYING ON INFORMATION FROM PARENTS</th>
<th>AGE RANGE</th>
<th>PURPOSE AND DESCRIPTION</th>
<th>SCORING</th>
<th>ACCURACY</th>
<th>TIME FRAME/COSTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant-Toddler Checklist (2002). Paul H. Brookes Publishing Co., Inc., P.O. Box 10624, Baltimore, MD 21285. (800-638-3775) ($99.95) <a href="http://www.brookespublishing.com">www.brookespublishing.com</a></td>
<td>6-24 mo</td>
<td>Purpose: Screening and surveillance of language and social milestones Description: Parents complete the Checklist's 24 multiple-choice questions. Focuses on screening for language, social communication. Examiners are encouraged to observe child to verify parents' answers via brief observation. Reading level is ~ 3rd grade. Can serve as an entry point into the assessment-level CSBS and also as a monitoring tool. Does not screen for motor milestones. In English, Spanish, Slovenian, Chinese, and German</td>
<td>Cutoff scores for each domain: social, speech and symbolic</td>
<td>By age and disability: i.e., developmental disabilities: Sensitivity: 78% Specificity: 84%</td>
<td>Scoring time: ~10 min (by hand), ~3 with CD-ROM Observation time: ~5 min Scoring Costs: $3.60-$12.00 Observation Costs: $6.00 Material Costs: $0.12 Total (Self-Report/Observation): $9.72-$18.12 Interview Time: 8 min Interview Costs: $9.60 Scoring/Materials + Observation: $9.72-$18.12 Total Interview Costs: $19.32-$28.72</td>
</tr>
<tr>
<td>Ages &amp; Stages Questionnaires: Social-Emotional (ASQ:SE) (2002). Paul H. Brookes Publishing Co., Inc., P.O. Box 10624, Baltimore, MD 21285 (800-638-3775) ($225.00) <a href="http://www.agesandstages.com">www.agesandstages.com</a></td>
<td>3-66 mo</td>
<td>Purpose: Screening and surveillance of milestones in social-emotional and mental health Description: Companion measure to ASQ-3. ASQ:SE consists of 8 age-specific forms (each 4-6 pages long) with 22-36 items. Items focus on self-regulation, compliance, communication, adaptive functioning, autonomy, affect, and interaction with people. Readability is 5th-6th grade. Includes activities sheets for families. In English and Spanish</td>
<td>Single cutoff score indicating when a referral is needed</td>
<td>By age and disability: i.e., social-emotional problems: Sensitivity: 71-85% Specificity: 90-98%</td>
<td>Scoring Time: 2 min Scoring Cost: $2.40 Material Costs: $0.24-$0.36 Total (Self-Report): $2.64-$2.76 Interview Time: 10 min Interview Cost: $12.00 Scoring/Materials: $2.64-$2.76 Total (Interview): $14.64-$14.76</td>
</tr>
</tbody>
</table>

Psychosocial Risk and Resilience Tools: Not all of the measures below are screens (meaning they do not provide definitive cutoffs) but instead assess a broad array of environmental risk and protective/resilience factors that may affect children’s developmental/mental health trajectory—well before delays become obvious. Lack of resilience factors or presence of risk factors, even if all aspects of development are typical at the moment, serve as a call to lower thresholds for referral and to consider a wide-range of community services (e.g., Head Start, parent training, parent mental health programs/parents’ own healthcare providers, social services).
<table>
<thead>
<tr>
<th>SURVEILLANCE TOOLS FOR RESILIENCE, RISK AND MENTAL HEALTH</th>
<th>AGE RANGE</th>
<th>PURPOSE AND DESCRIPTION</th>
<th>SCORING</th>
<th>ACCURACY</th>
<th>TIME FRAME/COSTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family Psychosocial Screen (FPS)</strong> (2000) Included within the AAP Pediatric Intake Form (<a href="http://www.brightfutures.org">http://www.brightfutures.org</a>), within PEDS: Developmental Milestones, and freely downloadable at <a href="http://www.pedstest.com/TheBook/Chapter10">www.pedstest.com/TheBook/Chapter10</a></td>
<td>Parent</td>
<td>Purpose: screening and surveillance of family psychosocial risk. Description: A 2-page clinic measure of psychosocial risk factors associated with developmental problems, often used for clinic intake. More than 4 risk factors is associated with developmental delays. The FPS also includes: (a) a 4 item screen for parental history of physical abuse as a child; (b) a 6 item measure of parental substance abuse; (c) a 4 item screen for domestic violence; and (d) a 3 item measure of maternal depression. Can be used along with the Brigance Parent-Child Interaction Scale to view parenting risk and resilience. Readability is 4th grade. In English and Spanish.</td>
<td>Refer/no refer to available community resources for each of the 4 screens’ risk factors</td>
<td>By condition, i.e., parental depression, substance abuse, etc. Depression (3 items): Sensitivity: 100%; Specificity: 88% Parental Substance Abuse (7 items): (a) alcohol abuse sensitivity ~90%; (b) drug abuse sensitivity ~88% Parent history of abusive punishment as a child (4 items): Sensitivity: 92-95%; Specificity: 87-92%</td>
<td>Scoring Time: 3 min Scoring Cost: $3.60 Material Costs: photocopied: $0.12 Laminated: $0.00 Total (Self-Report): $3.60-$3.72</td>
</tr>
<tr>
<td><strong>Brigance Parent-Child Interaction Scale (BPCIS)</strong> (2007) PEDSTest.com, LLC. The BPCIS is included in PEDS: Developmental Milestones and in the Brigance Infant and Toddler Screen. It can be freely downloaded at: <a href="http://www.pedstest.com/TheBook/Chapter10">http://www.pedstest.com/TheBook/Chapter10</a></td>
<td>0-30 mo</td>
<td>Purpose: Surveillance of parenting behaviors associated with resilience vs psychosocial risk. Description: Administered by parent-self report or examiner observation, the 18-19 multiple choice items tap whether parents read and talk with their child, enjoy talking with their child, and perceive him/her as interested in communication, whether parents actively teach their child new things, etc. Certain items are associated with resilience while others are associated with accumulating delays (which start to become visible at 6 mo of age and are striking by 12-18 mo).</td>
<td>Item analysis— discrete sets of items reflect resilience factors associated with typical development while others items reflect limited resilience associated with future or current delays</td>
<td>Not applicable</td>
<td>Scoring Time: 1 min Scoring Costs: $1.20 Materials: $0.06 Total (Self-Report): $1.26 Interview/Observation Administration time: ~5 min Interview Admin Costs: $6.00 Materials/Scoring ~$1.26 Total (Direct Admin): $7.26</td>
</tr>
<tr>
<td><strong>Strengths and Difficulties Questionnaire (SDQ)</strong> <a href="http://www.sdqinfo.org">http://www.sdqinfo.org</a></td>
<td>4-17 yr</td>
<td>Purpose: Resilience and psychosocial risk for mental health/social-emotional, behavioral skills. Description: 25 items (youth self-report vs parent or teacher report) tapping positive and negative attributes. Generates indicators for conduct problems, hyperactivity, emotional symptoms, peer problems and prosocial behavior. Produces a total strengths vs total difficulties score. Guidance is available on how to aggregate results for epidemiologic and needs-assessment studies. Cross-cultural research and translations are abundant and norming studies have been conducted in Great Britain, the United States and otherwise in European countries.</td>
<td>Comparison of factors</td>
<td>Not applicable</td>
<td>Scoring Time: 5 min Scoring Cost: $6.00 Materials: $0.12 Total (Self-Report): $6.12 Interview time: ~5 min Interview Admin costs: $6.00 Materials/Scoring: $0.12 Total (Direct Admin): $12.12</td>
</tr>
<tr>
<td>SCREENS FOR OLDER CHILDREN (These screens focus on academic skills and mental health, including ADHD screening)</td>
<td>AGE RANGE</td>
<td>PURPOSE AND DESCRIPTION</td>
<td>SCORING</td>
<td>ACCURACY</td>
<td>TIME FRAME/COSTS</td>
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<tr>
<td>Safety Word Inventory and Literacy Screener (SWILS)</td>
<td>6-14 yr</td>
<td>Purpose: Screening and surveillance of academic skills. Description: Children are asked (by parents or professionals) to read 29 common safety words (e.g., high voltage, wait, poison) aloud. The number of correctly read words is compared to a cutoff score. Results predict performance in math, written language, and a range of reading skills. Test content may serve as a springboard to injury prevention counseling and can be used to screen for parental literacy. Because even non-English speakers living in the United States need to read safety words in English, the measure is only available in English.</td>
<td>Single cutoff score by age, indicating the need for a referral.</td>
<td>By age/academic deficiencies: Sensitivity: 73-88%, Specificity: 77-88%</td>
<td>Scoring Time: 1 min, Scoring Costs: $1.20, Materials: ~$0.06, Total (Self-Report): $1.26, Administration time: ~7 min, Admin/Scoring Costs: $8.40, Materials/Scoring: ~$1.26, Total (Direct Admin): $9.66</td>
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<tr>
<td>Pediatric Symptom Checklist (PSC) (1991).</td>
<td>6-18 yr</td>
<td>Purpose: Screening and surveillance of emotional/mental health, and conduct. Serves as a necessary prescreen for sorting attention problems from competing conditions. Description: Administered by youth/parent self-report or by interview. The PSC/Pictorial PSC are 35 short statements of problem behaviors capturing various mental health challenges. The PSC-17/Pictorial PSC-17 are 17 item versions producing cutoffs for attention, internalizing, and externalizing factors. For the PSC, a single refer/nonrefer score; for the PSC-17/Pictorial PSC-17, cutoffs for attention, internalizing, and externalizing factors. PSC/Pictorial PSC by disability: i.e., mental problems of any kind, across numerous studies: Sensitivity: 80-95%, Specificity: 68-100% PSC-17/Pictorial PSC-17 by specific disability: i.e., ADHD: Sensitivity: 58%, Specificity: 91% Internalizing Disorders: Sensitivity: 52-73%, Specificity: 74% Externalizing Disorders: Sensitivity: 62%, Specificity: 89%</td>
<td></td>
<td>Scoring time: 3 min, Scoring Cost: $3.60, Materials: ~$0.06, Total (Self-Report): $3.66, Interview Time: 3 min, Interview Cost: $3.60, Materials/Scoring: $3.66, Total (Interview): $7.26</td>
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<tr>
<td>CRAFFT (Car, Relax, Alone, Forget, Friends, Trouble): (2009).</td>
<td>Adolescents (11-21 yr)</td>
<td>Purpose: To identify substance use (tobacco, alcohol or other drug abuse) in adolescents. Description: self-/youth-report questionnaire that contains 3 initial screening questions (A1, A2, A3). If the first 3 questions are all answered “no,” then providers should routinely ask 1 more question (B1). If 1 or more of the first 3 screening questions is positive/answered “yes,” then the provider should ask 6 more questions (CRAFFT: B1, B2, B3, B4, B5 and B6). If the CRAFFT score is 0 or 1 (0 or 1 item answered “yes”), then give brief advice only. If the CRAFFT score is &gt;2, then this is a positive screen and a brief assessment is needed. For scoring, refer to “description” Note: The AAP has published a recommended algorithm for substance abuse screening, assessment and intervention. Must be completed by youth confidentially.</td>
<td></td>
<td>Sensitivity: 76-93%, Specificity: 76-94% (positive predictive value [PPV] 29-83%) (negative predictive value [NPV] 91-98%) However, there is no cross cultural data (similar to the PSC and Pictorial PSC)</td>
<td>Scoring time: 1-2 min, Scoring cost: $1.20-$2.40, Materials: ~$0.06, Total (Self-Report): $1.26-$2.46, Interview time: 3 min, Interview cost: $3.60, Materials/Scoring: $3.66, Total (Interview): $4.86-$6.06, but higher if further counseling and intervention is needed</td>
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### ELECTRONIC RECORDS OPTIONS FOR SCREENING AND SURVEILLANCE WITH QUALITY TOOLS

**Description and Pricing**

**Chapter 16: Developmental-Behavioral Screening and Surveillance**

**Whole Family Developmental and Behavioral Monitoring System (CHADIS)**
- **Purpose:** Developmental-Behavioral Screening and Surveillance
- **Description:** CHADIS includes decision support for more than 75 both diagnostic and parent/family focused measures, such as the Vanderbilt ADHD Diagnostic Rating Scale, and various parent and adolescent depression, substance abuse, domestic violence and other inventories. CHADIS offers integration with existing electronic healthcare records (EHRs), works with a range of equipment/applications, and automatically generates reports. Pricing is via site license and ~$695 per year per full-time provider. Includes options for Maintenance of Certification (MOC), quality improvement (IQ) credit, and e-chapters for clinicians.
- **Screening and surveillance of developmental disability:** i.e., mental score; for the PSC-17, cutoffs for refer/nonrefer for the most commonly referred behaviors capturing various mental health externalizing factors (i.e., depression or anxiety) and internalizing problems (conduct, purpose).
- **Screening and surveillance of youth:** CRAFFT (Car, Relax, Alone, Forget, Purpose: abnormal screening and surveillance of youth, i.e., mental score; for the PSC-17, cutoffs for refer/nonrefer for the most commonly referred behaviors capturing various mental health externalizing factors (i.e., depression or anxiety) and internalizing problems (conduct, purpose).
- **Screening and surveillance of youth:** Patient Tools offers the ASQ (with audio option), ASQ:SE (with audio option), MCHAT, Peds, and the MCHAT for keyboard applications (allowing for actual comments from parents). Offers a parent portal (wherein families do not see the results). Scoring is automated as are summary reports for parents, referral letters when needed, and ICD-9/procedure codes. In English and Spanish. Health Level Seven (HL7)/Health Insurance Portability and Accountability Act (HIPPA)/Family Educational Rights and Privacy Act (FERPA) compliant integration with electronic records is available as is data export and aggregate views of records. $2.00-$2.75 per encounter (depending on volume).
- **Screening and surveillance of youth:** Webcasts/webinars—These are training options online, either live on a specific day and, eventually constantly available on publishers' websites.
- **Screening and surveillance of youth:** Ages and Stages-3 and ASQ: SE: Online administration and separately on a CD-ROM for offline administration with keyboards and tablet PCs
- **Screening and surveillance of youth:** Live training, online training

### Table 16-2 Annotated Description of Screening/Surveillance in Primary Care

**A. Elicit Parents’ Concerns**

At every visit, it is crucial to identify the parent/patient agenda, preferably prior to the encounter, so that clinicians can best prepare for the topics at hand. Informal questions to parents are rarely effective at eliciting their unique issues and do not render the decision support needed to discern which concerns are predictive of problems and which can be addressed with information and monitoring. It is best to use a standardized, validated screening/surveillance measure such as Peds which is also known to reduce problematic “oh, by the way” concerns, increase the likelihood of attendance at subsequent well-visits, and encourage referral uptake.

**B. Measure/Monitor Children’s Skills**

1. Use a broadband milestones-focused screen such as the ASQ or PEDS DM starting at 6-9 mo and at subsequent well-visits.
2. Use an autism-specific screen such as the M-CHAT at 18 and 24 mo and whenever clinical observation or parents’ concerns are worrisome. The requisite M-CHAT Follow-Up Interview (used after a failed M-CHAT) can become a request to referral sources.

**C. Measure/Monitor Psychosocial Risk Factors**

At the initial/intake visit (typically the 1st wk of life), a measure such as the Family Psychosocial Screen (FPS) is useful for identifying psychosocial and other risk factors (e.g., substance abuse, domestic violence, housing and food instability, parents’ education levels, parental mental and social health and support). Four or more risk factors in the ab and presence of intervention, generally lead to substantial declines in developmental–behavioral status. The FPS also contains a 3-item parental depression screen that should be re-administered twice in the 6-15 mo age range to identify and address issues with postpartum dysthymia.

**D. Measure/Monitor Parent–Child Interactions (Resilience Factors)**

Protective (also called resilience) factors are the positive parent–child interactions that promote developmental and behavioral skills (e.g., when parents actively and age-appropriately teach children new things, label objects of interest, share books, and converse with their child including back-and-forth sound play in infancy, playing peek-a-boo, etc.). Positive interactions often eclipse psychosocial risk factors and so it is helpful to measure both at the same time. A dearth of positive interactions takes a long-term toll on developmental–behavioral status with marked differences appearing as early as 12 mo of age. Although clinicians sometimes have opportunities to observe parent–child interactions, it is often easier to ask parents to complete a measure such as the Brigance Parent-Child Interactions Scale (BCPIS). Administration at 6 and again at 15 mo is recommended, along with parenting guidance and referrals for parent training when parents have not benefited from in-office advice.

**E. Identify/Update Family and Child Medical History and Biologic Risk Factors**

**Child’s Medical History:** Note in utero exposure to teratogenic/harmful substance, Apgar score less than 5 at 5 min, late or moderate preterm (>32 0/7 to 36 6/7 wk gestational age), very preterm (<32 wk gestational age, low birthweight (<2,500 g), very-low birthweight (<1,500 g), small for gestational age, in utero growth retardation; child’s history of: obesity, diabetes, or hypertension, congenital hydrocephalus, meningomyelocele, interventricular hemorrhage (grade III or IV), respiratory distress syndrome, anoxic brain injury, encephalopathy, genetic, metabolic or neurodevelopmental disorder with a high probability of a developmental delay, failure to thrive, iron-deficiency anemia, elevated blood lead level, vision or hearing impairment, HIV, congenital heart disease, obstructive sleep apnea, seizure disorder, etc.

**Family Medical/Developmental History:** Note any family history of language impairment, learning or intellectual disabilities, autism spectrum disorders, motor disorder, fragile X syndrome, attention-deficit/hyperactivity disorder, mental illness including anxiety disorder, major depression, bipolar disorder, history of deafness, genetic or metabolic disorders, cataract, retinoblastoma, retinal dysplasia, or glaucoma.

In most states, children are automatically eligible for IDEA services if they have a diagnosed condition involving biologic/malignant risk factors. In some states, IDEA programs serve children whose parents are mentally ill, intellectually disabled, as well as children in foster care because of a history of abuse or neglect.

**F. Conduct a Careful Physical Exam**

Identify any chronic respiratory or allergic illness, recurrent otitis, head trauma, and sleep problems including symptoms of obstructive sleep apnea. Attend to known symptoms of developmental–behavioral problems, including growth parameters, head shape, and circumference, especially in light of prior visits (e.g., failure to thrive, microcephaly or markedly decelerating head circumference, markedly accelerating head circumference or macrocephaly), facial and other body dysmorphology symptomatic of genetic conditions, eye findings (e.g., cataracts in various inborn errors of metabolism), vascular markings, testicular volume, and signs of neurocutaneous disorders (e.g., >6 café-au-lait spots in neurofibromatosis, hypopigmented macules in tuberous sclerosis), Lisch nodules, ash leaf macules, etc. Neurodevelopmental assessment should include muscle strength, joint laxity, tone, presence of abnormal reflexes, and disturbance of movement.

Focus carefully on physical findings suggestive of abuse or neglect and ensure prompt referrals to social work services.

Newborn hearing screening is essential but even the asymptomatic need follow-up with otoacoustic emissions (OAE) beginning at 6-mo of age and thereafter, as well as tympanometry to evaluate of middle ear pathology. Failed OAEs regardless of middle ear status require an axiomatic referral to an audiologist.

Assess vision at every visit: (a) Abnormal red reflex (may indicate cataract, glaucoma, retinoblastoma, retinal abnormality, or strabismus, or unequal or high refractive error); (b) abnormal ocular alignment (i.e., strabismus) or asymmetrical corneal light reflex; (c) pupillary asymmetry of ≥1 mm (suggestive of neurologic condition); (d) corneal asymmetry (suggestive of glaucoma); (e) unilateral ptosis or other lesions obstructing the visual axis (e.g., eyelid hemangioma), which may cause amblyopia; and (f) nystagmus. For children 3-4 yr of age, measures of visual acuity are needed for which the Lea Symbols are helpful because letter naming is not required. At age 5-6 yr, Snellen Eye Charts can be used. Prompt referral to a pediatric ophthalmologist is warranted when acuity is less than 20/40 in children ages 3-5 yr, or 20/30 in children ≥6 yr.

Lead screening should be provided whenever developmental–behavioral problems arise, but preferably for all children. Lead screening should be repeated at several points during the 0-6 yr age range. Children living in older homes, near busy streets, with pica, or recently immigrated are at particular risk, as are those who play with adult makeup.

Many of the above findings will automatically qualify children for IDEA Part C programs (birth-3) and so referral for early intervention should be axiomatic in such cases.
G. Provide Developmental–Behavioral Promotion

Whether or not screening/surveillance identifies problems, parents always need suggestions for what to do at home. The specifics of their concerns should be addressed with parenting information, advice on age-appropriate activities, and anticipatory guidance focused on how developmental changes affect health and safety (e.g., a baby about to crawl will find, mouth, and probably swallow small objects left under furniture). All parents need to be encouraged to promote their child’s language and preacademic/academic development. This is most easily accomplished with written patient education materials, by encouraging parents to visit websites with quality information, participating in Reach and Read, or by parent training classes, group well visits, or social work services. A well-organized system for filing and retrieving parent-focused materials is essential (see Table 16-3 for resources). Follow up with families, in 6-8 wk to assess the effectiveness of promotion activities, especially in-office advice about behavior and social skills. If less than successful, encourage parents to engage in more intensive services (e.g., parenting classes, family therapy). Information and referral resources are listed under the Resources section for this chapter.

H. Interpret Results, Explain Findings, Decide on Any Needed Referrals

Refer those at psychosocial risk and those with an absence of protective factors for Head Start/Early Head Start, quality daycare, or evidence-based parent-training programs. For all children with positive screens, refer to IDEA programs. Additionally, refer to autism specialty clinics if indicated.

Consider whether medical subspecialty referrals are needed. Electroencephalograms and neuroimaging are not routinely indicated but might be used if there is clinical suspicion of a seizure disorder, hydrocephalus, micro- or macrocephaly, encephalopathy, neurofibromatosis, tuberous sclerosis, brain tumor, or other neurologic problem (not including autism). Extreme handedness at an early age and persistence of fisting after 4 mo is another indicator of potential neuron migration disorders requiring imaging. Uncommonly, surveillance may indicate a need for additional metabolic screens, such as serum electrolytes and glucose, venous blood gas, serum ammonia, urine glycosaminoglycans, endocrine screens (e.g., thyroid-stimulating hormone, free thyroxine), creatinine kinase (CK), genetic testing (chromosomal analysis, DNA for fragile X, etc.), or screens for an infectious disease (e.g., HIV antibody testing, TORCH [toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex] infection testing). Because of the need to discern which tests are needed, referral to a developmental–behavioral or neurodevelopmental pediatrician is wise.

Gather referral information and then explain results to families. Sit down with them and describe referrals in a positive light (e.g., “There is much we can do to help.”). Avoid diagnostic labels because in all cases, further evaluation will be provided by referral services. Use euphemisms (e.g., “seems behind others,” “seems to be having difficulty with”) but use language strong enough that parents will take your concerns seriously. If at all possible, provide a take-home summary report. Most online screening services generate these automatically.

I. Document Findings and Make Referrals

A carefully constructed well-visit age-specific encounter form should have space to indicate measures administered and results. A longitudinal problem checklist should be used to briefly document results over time, intervention recommendations, (and will also help identify which measures are needed and when). Billing and coding for optimal reimbursement is essential (in many states, developmental–behavioral screening when coded properly, incurs separate reimbursement). A referral letter is also needed that can be shared with other programs. Be sure to document not only screens administered, results and observations but also health, hearing, and vision status; IDEA requires such information before evaluating children further. Online screening services generate referral letters and thus save a great deal of practice time and expense. If at all possible, make appointments for families because this greatly increases uptake. For examples of age-specific encounter forms, referral letters, and take-home parent summary reports, see www.pedstest.com/thebook.

J. Ensure a Medical Home

Children with health and developmental–behavioral problems often receive splintered care with little oversight from primary care providers who, in fact, should be the center of care coordination. Many families do not seek services in a timely manner and so it is critical to establish follow-up dates (e.g., on a longitudinal problem checklist) to determine whether recommendations were followed and whether additional screening or other encouragement is needed.

Establishing communication mechanisms with IDEA and other referral services is helpful so that personnel offer prompt updates on whether appointments were kept, results of further testing, and eligibility for services. Be aware that some referrals will not result in service eligibility due to deficits of insufficient severity. Note that in some, but not all states, IDEA programs for the birth-3 yr age-range can provide ongoing monitoring of ineligible children and suggest to parents other helpful resources. Prompt feedback on the issue of eligibility and ongoing monitoring is needed so that clinicians can refer to other types of intervention programs (e.g., quality daycare, Head Start, parenting training).

In any case, make sure to collaborate with non-medical services by establishing 2-way consent forms for sharing information. Clinicians should also identify communication preferences (e.g., by email, fax, or telephone [including available hours]) and the kind of information to be sent (e.g., evaluation reports, status updates, individual educational plans). Collaboration is facilitated if providers agree to advise intervention programs about medical conditions and medical interventions that may be needed at school.
Bibliography
Table 16-3 | Red Flags in Developmental Screening and Surveillance

| These indicators suggest that development is seriously disordered and that the child should be promptly referred to a developmental or community pediatrician. Note: Most children do not have “red flags” and thus require quality screening to detect any problems. |
| POSITIVE INDICATORS (THE PRESENCE OF ANY OF THE FOLLOWING) |
| Loss of developmental skills at any age |
| Parental or professional concerns about vision, fixing, or following an object or a confirmed visual impairment at any age (simultaneous referral to pediatric ophthalmology) |
| Hearing loss at any age (simultaneous referral for expert audiologic or ear, nose, and throat assessment) |
| Persistently low muscle tone or floppiness |
| No speech by 18 mo, especially if the child does not try to communicate by other means such as gestures (simultaneous referral for urgent hearing test) |
| Asymmetry of movements or other features suggestive of cerebral palsy, such as increased muscle tone |
| Persistent toe walking |
| Complex disabilities |
| Head circumference above the 99.6th centile or below 0.4th centile. Also, if circumference has crossed 2 centiles (up or down) on the appropriate chart or is disproportionate to parental head circumference |
| An assessing clinician who is uncertain about any aspect of assessment but thinks that development may be disordered |
| NEGATIVE INDICATORS (ACTIVITIES THAT THE CHILD CANNOT DO) |
| Sit unsupported by 12 mo |
| Walk by 18 mo (boys) or 2 yr (girls) (check creatine kinase urgently) |
| Walk other than on tiptoes |
| Run by 2.5 yr |
| Hold object placed in hand by 5 mo (corrected for gestation) |
| Reach for objects by 6 mo (corrected for gestation) |
| Point at objects to share interest with others by 2 yr |


Table 16-4 | Resources for Developmental–Behavioral Screening/Surveillance in Primary Care

**DEVELOPMENTAL–BEHAVIORAL PROMOTION AND PARENT TRAINING**

*Kids’ Health*

From the Nemours Foundation, this site has a well-visit guide for each age, anticipatory guidance information, and an easily searchable database for handouts (in English and Spanish) on health and safety, emotional and social development and positive parenting for babies through adolescence.

*Reach Out and Read*

Offers parenting handouts on how to share books, literacy milestones, and guidance for professionals. Tabs within the site include: Parents and Educators Home, Importance of Reading Aloud, Literacy Milestones, Reading Tips, Books for Children, and Books for Parents.

*American Academy of Pediatrics (Information for Families)*

The AAP has numerous handouts that can be downloaded for free and available in multiple languages. Provides information on a variety of topics including health conditions, safety and prevention, mental health issues from birth through adolescence.

*American Academy of Child and Adolescent Psychiatry*

AACAP was one of the first professional organizations to develop handouts for families. These are freely downloadable and cover a wide range of topics as divorce, sleep problems, specific mental health diagnoses, help for military families, and how and where to find a psychiatrist. Handouts are written in many different languages including Spanish, Malaysian, Urdu, Arabic, Icelandic, Polish, and Hebrew. Other site research reviews for professionals, video clips, and links to other resources.

**REFERRAL LINKS**

*American Academy of Pediatrics: Find a Pediatrician*

Helps locate developmental–behavioral, neurodevelopmental, general and other subspecialty pediatricians.

*Individuals with Disabilities Education Act*

Provides links to state, regional and local early intervention programs under the Individuals with Disabilities Education Act, and testing services for young children with suspected or known to have disabilities go to

*Early Head Start and Head Start*

Provides links to local programs including services for migrant workers, tribal councils, etc.

**INTERVENTION SERVICES FOR OLDER CHILDREN**

To refer children 3 yr of age and older for evaluations, contact the school district’s department of psychology or special education. For after school/tutoring programs, check with the child’s school of zone, and see the websites of the Boys and Girls Club and the YWCA.

**TRAINING AND IMPLEMENTATION PLANNING**

*Medical Home Initiative*

From the AAP and focused on coordinated care for children with special healthcare needs, the site has training materials, rating scales, an e-mail announcement list for providers, how-to information, etc. Medical Home also sponsors several conferences each year.

*Harvard University*

Includes a helpful video showing providers who, although reluctant to try quality screening, found use of tools far more sensitive and less than time-consuming. The site also provides a helpful implementation guide.

*PEDtest.org*

Includes downloadable implementation planning forms, workflow charts, two-way consent forms, longitudinal problem checklists, age-specific encounter forms, training guides, slide shows, freely downloadable risk and resilience measures, mental health and academic screens for older children, videos offering a rationale for screening, information about tools, guidance on billing and coding, and links to parenting resources in multiple languages.
Table 16-4 Resources for Developmental–Behavioral Screening/Surveillance in Primary Care—cont’d

<table>
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<th>ADDITIONAL RESOURCES</th>
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In the United States, 61% of all children younger than 5 yr—12.5 million children—were in regular childcare in 2011. Large proportions of young children are in childcare at all ages, with more children entering care as they get older; the majority of children 3 yr of age or older are in regular childcare. Young children of employed mothers spend on average 36 hr per wk in a childcare arrangement.

Childcare is affected by many factors, which derive from family demand, childcare supply, and child and family policy. With increasing movement of mothers into the workplace across the globe, the prime reason most families use childcare is to support maternal employment. At childbirth, unpaid maternity leave is the typical solution among U.S. mothers. The U.S. federal leave program allows for 12 wk of unpaid job-protected leave during pregnancy or after childbirth, but only covers approximately 50% of the workforce, as companies with <50 employees, part-time employees, and those working in informal labor markets are exempt. Four states and the District of Columbia have passed paid family leave laws. In part because of the financial burden of an unpaid maternity leave, many mothers return to work and their children begin childcare very young, sometimes in the 1st few wk after birth. In a 2000 Family and Medical Leave Act survey, only 10% of respondents reported taking more than 60 days for maternity leave. Approximately 44% of mothers in 2005-2007 were working by the time their first child was 3-4 mo of age, and approximately 63% of mothers were working by the time their first child was 12 mo of age. Some mothers face work requirements if they are receiving public benefits given the reforms to welfare passed by Congress in 1996. Many mothers feel strong financial motivation or even pressure to work, especially in single-parent households, or have strong incentive to work for short- and long-term financial security, interest and preference, or all of these. Maternal employment is not the only factor driving childcare use, as young children of unemployed mothers spend on average 21 hr per wk in childcare. Many parents want their children to have childcare experiences for the potential benefits early learning environments can give to their children, particularly preschoolers. Given these realities, childcare quality is of great concern, yet the quality of childcare and early education environments varies widely and the supply of high-quality childcare is largely deemed inadequate.

PROVISION AND REGULATION OF CHILDCARE IN AMERICA

Childcare Settings

Childcare settings vary widely and fall into 4 broad categories, here listed from the least to the most formal:

- Relative care;
- In-home nonrelative care such as nannies, babysitters, or au pairs;
- Family childcare, in which the caregiver provides care in her own home for up to 6 young children often including children of mixed ages, siblings, or the provider’s own children; and
- Center-based care, provided in nonresidential facilities for children grouped by age.

Parents more often utilize home-based care for infants and toddlers, partly because of greater preference, flexibility, and availability, and sometimes because of lower cost. Use of center-based childcare is greater among preschoolers (children 3-5 yr old). Childcare centers and early education programs are administered by a wide array of businesses and organizations, including for-profit independent companies and chains, religious organizations, public and private schools, community organizations, cooperatives, and public agencies. Preschool programs (e.g., Head Start, prekindergarten) also may play an important role in childcare. Although early education programs may have a greater focus on educational activities and often only provide limited hours of care per days, the health and safety issues involved with preschool programs are similar to those presented by other group childcare settings.

Childcare Licensing, Regulation, and Accreditation

Licensing and regulatory requirements for the most part mandate basic health and safety standards, such as sanitary practices, child and caregiver education and training requirements. Most childcare centers and preschools and many family daycare providers are subject to state licensing and regulation. As of this writing, with the exception of Idaho, all states regulate centers, as does the District of Columbia (for the most recent data, see http://www.naralicensing.org/Licensing). Most states also regulate family childcare providers, although some states only license specific types of family childcare homes, and 3 states do not license these providers at all (Idaho, Louisiana, and New Jersey). Seven states (Arizona, Idaho, Louisiana, New Jersey, Ohio, South Dakota, and Virginia) do not license small family childcare homes, and 11 states (Arkansas, Idaho, Kentucky, Louisiana, Maryland, Maine, North Carolina, New Jersey, Vermont, Washington, and Wisconsin) and the District of Columbia do not license large/group family childcare homes. Louisiana has a registration process for family childcare centers and preschools and many family daycare providers are subject to state licensing and regulation. As of this writing, with the exception of Idaho, all states regulate centers, as does the District of Columbia (for the most recent data, see http://www.naralicensing.org/Licensing). Licensing and regulatory requirements for the most part mandate basic health and safety standards, such as sanitary practices, child and caregiver education and training requirements. Most childcare centers and preschools and many family daycare providers are subject to state licensing and regulation. As of this writing, with the exception of Idaho, all states regulate centers, as does the District of Columbia (for the most recent data, see http://www.naralicensing.org/Licensing). Most states also regulate family childcare providers, although some states only license specific types of family childcare homes, and 3 states do not license these providers at all (Idaho, Louisiana, and New Jersey). Seven states (Arizona, Idaho, Louisiana, New Jersey, Ohio, South Dakota, and Virginia) do not license small family childcare homes, and 11 states (Arkansas, Idaho, Kentucky, Louisiana, Maryland, Maine, North Carolina, New Jersey, Vermont, Washington, and Wisconsin) and the District of Columbia do not license large/group family childcare homes. Louisiana has a registration process for family childcare homes with no more than 6 children, but registration is only required when the provider cares for children subsidized by the federal Childcare and Development Fund (which assists low-income families receiving temporary public assistance, or those needing childcare in order to work or receiving training to transition off of public assistance). New Jersey has a voluntary registration process for family childcare homes that is operated by childcare resource and referral agencies in the state.
Many providers are legally exempt from licensing standards. Exemptions for various types of programs vary by state. The smallest homes (3-4 children in care) are typically license-exempt, encompassing relative, friend, and neighbor caregivers as well as babysitters, nannies and au pairs. These providers fall outside of any regulatory scrutiny, and some may not even think of themselves as offering “childcare”; 31% of 9 mo olds and 22% of 2 yr olds may be in small home-based care settings (3 or fewer children). Fewer are cared for in large home-based settings (4 or more children), typically by nonrelatives. Small family childcare homes are exempt if there is a small number of children in care in 26 states, and large/group family childcare homes are exempt if they are open part-day in 11 states. Unlike exemption rules for homecare providers, which typically are based on size, centers are often exempted if overseen by other organizations such as schools, churches, or local governments, and thus have some external oversight. Many of these entities provide part-day or part-week Head Start or preschool programs, and about half of the states also explicitly exempt such part-time programs. Just 9% of 9 mo olds and 17% of 2 yr olds were cared for in centers. In contrast to care for 4 yr olds (when more than half of children are in center care), few centers caring for younger children were exempt from licensing (35% of centers caring for 4 yr olds were not licensed in contrast to 2% of centers caring for 2 yr olds).

Homes and centers that fall under state licensing guidelines face very different requirements. Size differs greatly between the 2 types of contexts, and such size differences are built into regulations in terms of the maximum number of children that can be cared for in a group and the number of adults that must be present. The most common state-required maximum group size in centers is 8 for infants, 12 for toddlers, and 20 for preschoolers; centers may have numerous classrooms of these sizes. For centers, regulations explicitly state an allowable ratio of children to adults. The most common ratios are 4:1 for infants, 6:1 for toddlers, and 10:1 for preschoolers, meaning that typically there would be 2 adults in a group. States license homes in 2 categories, small and large, with typical maximums of 6 and 12 in the 2 categories (including the provider’s own children). More than three-quarters of licensed homes fall within the small category. Thus the total size of a typical home is smaller than just 1 classroom in a center. States less often explicitly lay out child-to-adult ratios for homes, given that many homes involve 1 provider caring for all of the children. Some states restrict the number of younger children that may be in care, or explicitly provide ratios (especially for large homes), although these restrictions vary greatly across states.

Health and safety conditions may be unsatisfactory in unlicensed settings. In most states, licensing and regulatory standards have been found to be inadequate to promote optimal child development, and in many states standards are so low as to endanger child health and safety. Therefore, even licensed providers may be providing care at quality levels far below professional recommendations. A small portion of providers become accredited by National Association for the Education of Young Children (NAEYC), National Association for Family Child Care (NAFCC), or other organizations by voluntarily meeting high-quality, developmentally appropriate, professionally recommended standards. The accreditation process goes far beyond health and safety practices and structural and caregiver characteristics to examine the quality of child–caregiver interactions, which are crucial for child development, as described in the next section. Evidence indicates that childcare programs that complete voluntary accreditation through NAEYC improve in quality and provide an environment that better facilitates children’s overall development. Only 10% of childcare centers and 1% of family childcare homes are accredited; this is partly the result of a lack of knowledge, resources, and incentives for providers to improve quality, but it may also be partly because of expenses providers incur in the process of becoming accredited.

State childcare licensing agencies are playing a larger role in various initiatives designed to improve the quality of childcare, working through the infrastructure of the early care and education system. Several states’ licensing agencies are part of quality initiatives called quality ratings and improvement systems, such as tiered quality strategies (e.g., tiered reimbursement systems for participating providers who achieve levels of quality beyond basic licensing requirements), public funding to facilitate accreditation, professional development systems, and program assessments and technical assistance.

Sick Children

When children are ill, they may be excluded from out-of-home arrangements, and settings under state licensure are required to exclude children with certain conditions. Guidelines for health and safety in out-of-home care from the American Academy of Pediatrics, the American Public Health Association, and the National Resource Center for Health and Safety in Child Care and Early Education offer recommendations regarding the conditions under which sick children should and should not be excluded from group programs (Table 17-1). State laws typically mirror these guidelines but may be stricter in some states.

Most families need to make arrangements to keep sick children at home (such as staying home from work or having backup plans with an alternative caregiver). Alternative care arrangements outside the home for sick children are relatively rare but may include either (1) care in the child’s own center, if it offers special provisions designed for the care of ill children (sometimes called the infirmary model or sick daycare), or (2) care in a center that serves only children with illness or temporary conditions. Although it is important that such arrangements emphasize preventing further spread of disease, one study found no occurrence of additional transmission of communicable disease in children attending a sick center. The impact of group care of ill children on their subsequent health and on the health of their families and community is unknown.

ChilDCARE’S ROLE IN CHILD HEALTH AND DEVELOPMENT

Characteristics of Childcare and Associations with Child Developmental Outcomes

High-quality childcare is characterized by warm, responsive, and stimulating interactions between children and caregivers. In high-quality interactions, caregivers express positive feelings toward their children; are emotionally involved, engaged, and aware of the child’s needs and sensitive and responsive to their initiations; speak directly with children in a manner that is elaborate and stimulating while being age-appropriate; and ask questions and encourage children’s ideas and verbalizations. Structural quality features of the setting, including ratio of children to adults, group size, and caregiver education and training, act indirectly on child outcomes by facilitating high-quality child–caregiver interactions. It would be difficult for even the most sensitive and stimulating provider to engage in high-quality interactions with each child, if the provider was the sole caregiver of 10 toddlers.

The quality, quantity, type of setting, and stability of childcare experienced by young children contribute to child development. Childcare use by itself does not affect mother–child attachment. Only when combined with low maternal sensitivity and responsiveness does poor-quality childcare, larger quantities of childcare, or multiple childcare arrangements predict greater likelihood of insecure attachment.

Adjusting for family factors (i.e., parental income, education, race/ethnicity, family structure, parental sensitivity) the quality of childcare has a unique and consistent, albeit small, association with child outcomes across most domains of development. The type of childcare setting has unique effects, controlling for quality, with results from numerous studies demonstrating that center-based care is associated with better language and preacademic performance than home-based care. Quantity of care (hours per week) may also have unique effects, but findings are mixed, with some studies demonstrating small associations between greater quantity and elevated behavior problems, and other studies finding no associations for most children. Instability in childcare—over the course of a day, such as with rotating staff or multiple arrangements, or over time, with frequent changes in arrangements—does have negative effects on children’s language and internalizing problems. Also, as childcare settings naturally have packages of quality characteristics, which are a mix of lower- and
Table 17-1  Conditions That Do and Do Not Require Exclusion from Group Childcare Settings

<table>
<thead>
<tr>
<th>CONDITIONS THAT REQUIRE EXCLUSION</th>
<th>COMMENTS</th>
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<tbody>
<tr>
<td>If any of these 3 key criteria for exclusion of children who are ill are met, the child should be temporarily excluded, regardless of the type of illness:</td>
<td>Provider should specify in their policies, approved by the facilities’ healthcare consultant, what severity level of illness the facility can manage, and how much and what types of illness will be addressed:</td>
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<tr>
<td>Illness preventing the child from participating comfortably in activities as determined by the childcare provider</td>
<td>• Severity level 1 consists of children whose health condition is accompanied by high interest and complete involvement in activity associated with an absence of symptoms of illness (such as children recovering from pinkeye, rash, or chickenpox), but who need further recuperation time.</td>
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<td></td>
<td>• Severity level 2 encompasses children whose health condition is accompanied by a medium activity level because of symptoms (such as children with low-grade fever, children at the beginning of an illness, and children in the early recovery period of an illness).</td>
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<td>• Severity level 3 is composed of children whose health condition is accompanied by a low activity level because of symptoms that preclude much involvement.</td>
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<tr>
<td>Illness resulting in a greater need for care than the childcare staff can provide without compromising the health and safety of the other children as determined by the childcare provider</td>
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<tr>
<td>Illness that poses a risk of spread of harmful diseases to others</td>
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<tr>
<td>In addition to the above key criteria, temporary exclusion is recommended when the child has any of the following conditions:</td>
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<td>Fever (temperature above 38°C [101°F] orally, above 38.9°C [102°F] rectally, or above 37.8°C [100°F] or higher taken axillary [armpit] or measured by an equivalent method) and behavior change or other signs and symptoms (e.g., sore throat, rash, vomiting, diarrhea)</td>
<td>Accompanied by behavior changes or other signs or symptoms of illness until medical professional evaluation finds the child able to be included at the facility</td>
</tr>
<tr>
<td>Acute change in behavior including lethargy/lack of responsiveness, inexplicable irritability or persistent crying, difficult breathing, or having a quickly spreading rash</td>
<td>Until evaluation by a medical professional finds the child able to be included at the facility.</td>
</tr>
<tr>
<td>Diarrhea (defined by watery stools or decreased form of stool that is not associated with changes of diet). Exclusion is required for all diapered children whose stool is not contained in the diaper and toilet-trained children if the diarrhea is causing soiled pants or clothing</td>
<td>Readmission after diarrhea can occur when diapered children have their stool contained by the diaper (even if the stools remain loose) and when toilet-trained children are continent. Special circumstances that require specific exclusion criteria include the following:</td>
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<td></td>
<td>• Toxin-producing <em>Escherichia coli</em> or <em>Shigella</em> infection, until stools are formed and test results of stool cultures obtained from stools produced 24-hr apart do not detect these organisms.</td>
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<tr>
<td></td>
<td>• <em>Salmonella</em> serotype Typhi infection, until diarrhea resolves and, in children younger than age 5 yr, 3 negative stool cultures obtained with 24-hr-intervals are obtained.</td>
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<tr>
<td>Blood or mucus in stool</td>
<td>Not explained by dietary change, medication, or hard stools.</td>
</tr>
<tr>
<td>Vomiting illness</td>
<td>More than 2 times in the previous 24 hr, unless the vomiting is determined to be caused by a noninfectious condition and the child remains adequately hydrated.</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Persistent (continues more than 2 hr) or intermittent associated with fever or other signs or symptoms.</td>
</tr>
<tr>
<td>Mouth sores with drooling</td>
<td>Unless the child’s primary care provider or local health department authority states that the child is noninfectious.</td>
</tr>
<tr>
<td>Rash with fever or behavior changes</td>
<td>Until the primary care provider has determined that the illness is not an infectious disease.</td>
</tr>
<tr>
<td>Active tuberculosis</td>
<td>Until the child’s primary care provider or local health department states child is on appropriate treatment and can return.</td>
</tr>
<tr>
<td>Impetigo</td>
<td>Until treatment has been started.</td>
</tr>
<tr>
<td>Streptococcal pharyngitis (i.e., strep throat or other streptococcal infection)</td>
<td>Until 24 hr after treatment has been started.</td>
</tr>
<tr>
<td>Purulent conjunctivitis</td>
<td>Defined as pink or red conjunctiva with white or yellow eye discharge, until after treatment has been initiated.</td>
</tr>
<tr>
<td>Pediculosis (head lice)</td>
<td>Until after the first treatment Note: Exclusion is not necessary before the end of the program day</td>
</tr>
<tr>
<td>Scabies</td>
<td>Until after treatment has been given.</td>
</tr>
</tbody>
</table>
higher-quality indicators, the bundle of features in a childcare arrangement may be another meaningful way for a parent to consider the potential effects of an arrangement on their child.

When a healthcare provider talks with a parent about the parent’s child’s childcare arrangement, it is also important to consider the individual child’s characteristics, health concerns, dispositions, and even physiologic responses to the environment. Like all environments, childcare is experienced differently by different children. An average environment can often sufficiently compensate for the typical regulatory capacities of most children, but when an environment lacks adequate support for a child’s unique needs, healthy development can be further compromised. Some children may be more vulnerable to bad childcare (or particularly responsive to good childcare), such as children with difficult or fearful temperaments, especially if their home environments are characterized by more risk factors, such as poverty or high conflict with a parent.

Several large studies have found that most U.S. childcare is of “poor to mediocre” quality. In one study, only 14% of centers (8% of
center-based infant care) were found to provide developmentally appropriate care, while 12% scored at minimal levels that compromised health and safety (40% for infant care). In another study, 58% of family daycare homes provided adequate or custodial care, and only 8% provided good care. Children with the greatest amount of family risk may be the most likely to receive childcare that is substandard in quality. Many children from lower-risk families also receive lower-quality care, and despite their advantages at home, these children may not be protected from the negative effects of poor-quality care.

Affordable, accessible, high-quality childcare is hard to find. Middle-class families spend approximately 6% of their annual income on childcare expenses, whereas poor families spend approximately 33% (on par with housing expenses). Infant and toddler care is particularly expensive with fewer available slots. For a married couple with children, the average cost of full-time center care for 1 infant ranges from 7% to approximately 19% of the state median income, depending on the state, and the average cost of center care for one 4 yr old exceeds 10% of the median household income in 21 states and the District of Columbia. For single parents, the average cost of center-based infant care exceeds 25% of median income in every state. The average cost of family childcare is only slightly lower.

In addition to the stress of meeting such a high expense, many parents worry that their child will feel unhappy in group settings, will suffer from separation from the parents, or will be subjected to neglect or abuse. This worry is especially likely among low-income parents with more risk factors, fewer resources, and fewer high-quality options available. Parents are the purchasers but not the recipients of care, and are not in the best position to judge its quality. Many parents are first-time purchasers of childcare with little experience and very immediate needs, selecting care in a market that does little to provide them with useful information about childcare arrangements. In many states, efforts are underway to improve quality and provide parents with quality information, but several states do not have a quality rating and information system, and programs in states that do are still emerging, and testing of effectiveness is still underway. To inform their care decisions, parents may turn to their child's pediatrician as the only professional with expertise in child development with whom they have regular and convenient contact.

**Childcare and Child Health**

A disproportionate number of sudden infant death syndrome (SIDS) deaths occur in childcare centers or family-based childcare homes (approximately 20%). Infants who are back-sleepers at home, but are put to sleep on their backs in childcare settings, have a higher risk of SIDS. Providers and parents should be made aware of the importance of placing infants on their backs to sleep (see Chapter 37).

Children enrolled in childcare are also of an age that places them at increased risk for acquiring infectious diseases. Participation in group settings elevates exposure. Children enrolled in such settings have a higher incidence of illness (upper respiratory tract infections, otitis media, diarrhea, hepatitis A infections, skin conditions, and asthma) than those cared for at home, especially in the preschool years; these illnesses have no long-term adverse consequences. Childcare providers that follow childcare licensure guidelines for handwashing, diapering, and food handling, and that manage child illness appropriately, can reduce communicable illnesses.

There is debate about whether childcare exposure serves as a risk or protective factor for asthma. One cross-sectional study found that preschoolers in childcare had increased risk of the common cold and otitis media, and children who began childcare before the age of 2 yr had increased risk of developing recurrent otitis media and asthma. However, a longitudinal study found that children who were exposed to older children at home or to other children at childcare during the 1st 6 mo of life were less likely to have frequent wheezing from age 6–13 yr, suggesting that childcare exposure may protect against the development of asthma and frequent wheezing later in childhood. A 10 yr follow-up of a birth cohort found no association between childcare attendance and respiratory infections, asthma, allergic rhinitis, or skin prick test reactivity. Another study found that in the 1st yr of elementary school, children who had attended childcare had fewer absences from school, half as many episodes of asthma, and less acute respiratory illness than their peers who had never attended childcare. These results are perhaps related to protection against respiratory illness as a result of early exposure or a shift in the age-related peak of illness, though selection of illness-prone children into home care may play a role. Other factors may also be relevant to this issue, such as children in childcare potentially being less exposed to passive smoking than children at home.

**Childcare and Children with Special Needs**

The needs of children with mental, physical, or emotional disabilities who, because of their chronic illness, require special care and instruction may require particular attention when it comes to their participation in most childcare settings. Guiding principles of services for children with disabilities advocate supporting children in natural environments, including childcare. Furthermore, the Americans with Disabilities Act and Section 504 of the Rehabilitation Act of 1973 prohibit discrimination against children and adults with disabilities by requiring equal access to offered programs and services.

Although many childcare providers and settings are unprepared to identify or administer services for children with special needs, childcare could be utilized for delivery of support services to these children and/or for linking families to services, such as early intervention and doctor referrals. Furthermore, pediatricians can draw upon childcare providers to help provide important evaluative data regarding a child's well-being, as these providers have extensive daily contact with the child and may have broad, professional understanding of normative child development. A childcare provider may be the first to identify a child's potential language delay. Childcare providers are also necessary and valuable partners in the development and administration of early intervention service plans.

Children with special needs may be eligible for services under the Individuals with Disabilities Education Act (IDEA) (see Chapter 36). The purpose of this law is to provide "free appropriate public education," regardless of disability or chronic illness, to all eligible children, birth to 21 yr, in a natural and/or least-restrictive environment. Eligible children include those with mental, physical, or emotional disabilities who, because of their disability or chronic illness, require special instruction to learn. As a part of these services, a formal plan of intervention is to be developed by the service providers, families, and the children's healthcare providers. Federal funds are available to implement a collaborative early intervention system of services for eligible infants and toddlers below the ages of birth and 3 yr and their families. These services include screening, assessment, service coordination, and collaborative development of an individualized family service plan (IFSP). The IFSP describes early intervention services for the infant or toddler and family, including family support and the child's health, therapeutic, and educational needs. An understanding of the child's routines and real-life opportunities and activities, such as eating, playing, interacting with others, and working on developmental skills, is crucial to enhancing a child's ability to achieve the functional goals of the IFSP. Therefore it is critical that childcare providers be involved in IFSP development or revision, with parental consent. Childcare providers should also become familiar with the child's IFSP and understand the providers' role and the resources available to support the family and childcare provider.

Additionally, IDEA provides support for eligible preschool age children to receive services through the local school district. This includes development of a written individualized education program (IEP), with implementation being the responsibility of the local education agency in either a public or private preschool setting. As with IFSPs, childcare providers should become familiar with the preshooler's special needs as identified in the IEP and may become involved, with parental consent, in IEP development and review meetings. In cases where children may have or be at risk of developmental delays, a diagnosis is important for obtaining and coordinating services and further evaluation. To this end, pediatricians can partner with childcare providers to screen and monitor children's behavior and development.
**Table 17-2** Childcare Information Resources

<table>
<thead>
<tr>
<th>ORGANIZATION</th>
<th>SPONSOR</th>
<th>WEBSITE AND CONTACT INFORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child Care Aware</td>
<td>Child Care Aware of America (formerly National Association of Child Care Resource and Referral Agencies)</td>
<td><a href="http://www.childcareaware.org">http://www.childcareaware.org</a></td>
</tr>
<tr>
<td>Healthy Child Care America</td>
<td>American Academy of Pediatrics (AAP)</td>
<td><a href="http://www.healthychildcare.org">http://www.healthychildcare.org</a></td>
</tr>
<tr>
<td>National Association for the Education of Young Children (NAEYC)</td>
<td></td>
<td><a href="http://www.naeyc.org">http://www.naeyc.org</a></td>
</tr>
<tr>
<td>National Association for Sick Child Daycare (NASCD)</td>
<td></td>
<td><a href="http://www.nascd.com">http://www.nascd.com</a></td>
</tr>
<tr>
<td>National Association for Family Child Care (NAFCC)</td>
<td></td>
<td><a href="http://www.nafcc.org">http://www.nafcc.org</a></td>
</tr>
<tr>
<td>National Resource Center for Health and Safety in Child Care and Early Education (NRC)</td>
<td></td>
<td><a href="http://www.nrckids.org">http://www.nrckids.org</a></td>
</tr>
</tbody>
</table>

**ROLE OF PEDIATRIC PROVIDERS IN CHILDCARE**

**Advising Parents on Childcare Selection**

Organized professional guidance in choosing childcare is insufficient. Pediatricians can help parents understand the importance for their child’s development of selecting high-quality care by describing how it looks and providing referrals and tips on how to find and select high-quality childcare (Table 17-2). In addition, pediatricians can help parents determine how to adjust childcare arrangements to best meet their child’s specific needs (e.g., allergies, eating and sleeping habits, temperament and stress-regulation capacities). For most parents, finding childcare that they can afford, access, manage, and accept as a good environment for their child is a very difficult process and one many parents find distressing. Many parents are also worried about how their child will fare in childcare (e.g., Will their child feel distressed by group settings, suffer from separation from the parents, or even be subjected to neglect or abuse?). These worries are especially likely among low-income parents with fewer family and community resources to draw upon. A few parents may think of childcare only as babysitting, and may not consider the consequences for their child’s cognitive, linguistic, and social development, focusing solely on whether the child is safe and warm. These parents may be less likely to select a high-quality childcare arrangement, which is especially problematic if the family is facing socioeconomic challenges that already place them at risk of receiving lower-quality care for their children. For these parents, it is vital to stress the importance of quality and its implications for their child’s cognitive, language, and behavioral development and school readiness.

**Advising Parents on Childcare Health Issues**

Parents of infants should be advised to ensure that childcare providers put infants on their back to sleep to prevent SIDS. Also, pediatricians should emphasize the importance of following vaccination schedules; most states require compliance for children to participate in licensed group childcare settings.

When children are ill, parents should be advised to follow guidelines for inclusion and exclusion (see Table 17-1). Parents may disagree with childcare staff about whether a child meets or does not meet the exclusion criteria. However, professional guidelines state that “if … the reason for exclusion relates to the child’s ability to participate or the caregiver/teacher’s ability to provide care for the other children, the caregiver/teacher should not be required to accept responsibility for the care of the child.” (http://nrckids.org/index.cfm/products/stepping-stones-to-caring-for-our-children-3rd-edition-ss3/stepping-stones-to-caring-for-our-children-3rd-edition-ss3/).

**Helping Children with Special Needs**

Pediatricians should work with parents and communicate with other service providers and early intervention staff to identify problems, remove access barriers, and coordinate service delivery for children with special needs. They should also encourage involvement of parents and childcare providers in IFSP or IEP plan development.

**Consulting and Partnering with Childcare Providers**

Most state regulations mandate that licensed programs have a formal relationship with a healthcare provider. Additional state efforts include mental health consultation models to support providers, who are often not well trained in managing child behavior, and build capacity to raise quality for all children. Early childhood mental health consultation links a mental health professional with an early education and care provider in an ongoing problem-solving and capacity-building relationship. Pediatricians can provide consultation to childcare providers about measures to protect and maintain the health and safety of children and staff. This may include consultation regarding promoting practices to prevent SIDS; preventing and reducing the spread of communicable disease; reducing allergen, toxin, and parasite exposure; ensuring vaccinations for children and staff; removing environmental hazards; and preventing injuries.

Bibliography is available at Expert Consult.
has been found to be associated with negative parent functioning, such as parental depression and feelings of incompetence, negative child behavior, such as noncompliance and whining, and negative parent–child interaction, such as inconsistent discipline, decreased communication, and decreased affection. Greater childhood distress is associated with greater parental distress. Continued parental conflict and loss of contact with the noncustodial parent, usually the father, is common. Two of the most important factors that contribute to morbidity of the children in a divorce include parental psychopathology and disrupted parenting before the separation. The year following the divorce is the period when problems are most apparent; these problems tend to dissipate over the next 2 yr. Depression may be present 5 yr later, and educational or occupational decline may occur even 10 yr later. It is difficult to sort out all of the confounding factors. Children may suffer when exposed to parental conflict that continues after divorce, and in some cases may escalate. The degree of interparental conflict may be the most important factor associated with child morbidity. A continued relationship with the noncustodial parent, as long as there is minimal interparental conflict, was a factor associated with more positive outcomes.

School-age children may respond with evident depression, may seem indifferent, or may be markedly angry. Other children appear to deny or avoid the issue, behaviorally or verbally. Most children cling to the hope that the actual placement or separation is not real and are only temporary. The child may experience guilt by feeling that the loss, separation, or placement represents rejection and perhaps punishment for misbehavior. Children may protect a parent and assume guilt, believing that their own “badness” caused the parent to depart. Outwardly blaming parents may be perceived by a child as emotionally risky; parents who discover that a child harbors resentment might punish the child further for these thoughts or feelings. Children who feel that their misbehavior caused their parents to separate or become divorced have the fantasy that their own trivial or recurrent behavioral patterns caused their parents to become angry at each other. Some children have behavioral or psychosomatic symptoms and unwittingly adopt a “sick” role as a strategy for reuniting their parents.

In response to divorce of parents and the subsequent separation and loss, older children and adolescents commonly show intense anger. Five yr after the breakup, approximately 3% of children report intense unhappiness and dissatisfaction with their lives and their reconfigured families, another 3% show clear evidence of a satisfactory adjustment, whereas the remaining 3% demonstrate a mixed picture, with good achievement in some areas and faltering achievement in others. After 10 yr, approximately 45% do well, but 40% may have academic, social, and/or emotional problems. As adults, some are reluctant to form intimate relationships, fearful of repeating their parents’ experience. Parental divorce has a moderate long-term negative impact on the adult mental health status of children who had experienced it, even after controlling for changes in economic status and problems before divorce. Good adjustment of children after a divorce is related to ongoing involvement with 2 psychologically healthy parents who minimize conflict, and to the siblings and other relatives who provide a positive support system. Divorcing parents should be encouraged to avoid adversarial processes and to use a trained mediator to resolve disputes if needed. Joint custody arrangements may reduce ongoing parental conflict, but children in joint custody may feel overburdened by the demands of maintaining a strong presence in 2 homes.

When the primary care provider is asked about the effects of divorce, parents should be informed that different children may have different reactions, but that the parents’ behavior and the way they interact with each other will have a major and long-term effect on the child’s adjustment. The continued presence of both parents in the child’s life, with minimal interparental conflict, is most beneficial to the child.

**MOVE/FAMILY RELOCATION**

A significant proportion of the population of the United States changes residence each year. The effects of this movement on children and families are frequently overlooked. For children, the move is essentially involuntary and out of their control. When such changes in family
structure as divorce or death precipitate moves, children face the stresses created by both the precipitating events and the move itself. Parental sadness surrounding the move may transmit unhappiness to the children. Children who move lose their old friends, the comfort of a familiar bedroom and house, and their ties to school and community. They not only must sever old relationships but also are faced with developing new ones in new neighborhoods and new schools. Children may enter neighborhoods with different customs and values, and because academic standards and curricula vary among communities, children who have performed well in one school may find themselves struggling in a new one. Frequent moves during the school years are likely to have adverse consequences on social and academic performance.

Migrant children and children who emigrate from other countries present with special circumstances. These children not only need to adjust to a new house, school, and community but also need to adjust to a new culture and, in many cases, a new language. Because children have faster language acquisition than adults, they may function as translators for the adults in their families. This powerful position may lead to role reversal and potential conflict within the family. In the evaluation of migrant children and families, it is important to ask about the circumstances of the migration, including legal status, violence or threat of violence, conflict of loyalties, and moral, ethical, and religious differences.

Parents should prepare children well in advance of any move and allow them to express any unhappy feelings or misgivings. Parents should acknowledge their own mixed feelings and agree that they will miss their old home while looking forward to a new one. Visits to the new home in advance are often useful preludes to the actual move. Transient periods of regressive behavior may be noted in preschool children after moving, and these should be understood and accepted. Parents should assist the entry of their children into the new community, and whenever possible, exchanges of letters and visits with old friends should be encouraged.

SEPARATION BECAUSE OF HOSPITALIZATION
Potential challenges for hospitalized children include coping with separation, adapting to the new hospital environment, adjusting to multiple caregivers, seeing very sick children, and sometimes experiencing the disorientation of intensive care, anesthesia, and surgery. To help mitigate potential problems, a preadmission visit to the hospital is important to allow the child to meet the people who will be offering care and ask questions about what will happen. Parents of children younger than 5-6 yr of age should room with the child if feasible. Older children may also benefit from parents staying with them while in the hospital, depending on the severity of their illness. Creative and active recreational or socialization programs with child life specialists, chances to act out feared procedures in play with dolls or mannequins, and liberal visiting hours, including visits from siblings, are all helpful. Sensitive, sympathetic, and accepting attitudes toward children and parents by the hospital staff are very important. Healthcare providers need to remember that parents have the best interest of their children at heart and know their children the best. Whenever possible, school assignments and tutoring for the hospitalized children should be available in order to engage the child intellectually and prevent them from falling behind in their scholastic achievements.

The psychologic aspects of illness should be evaluated from the outset, and physicians should act as a model for parents and children by showing interest in a child’s feelings, allowing them a venue for expression, and demonstrating that it is possible and appropriate to communicate discomfort in verbal, symbolic language. Continuity of medical personnel may be reassuring to the child and family.

MILITARY FAMILIES
More than 2 million children live in military families in the United States, and approximately 50% of them obtain medical care in the community rather than at a military medical facility. Children whose parents are serving in the military may experience loss and separation in multiple ways. These include frequent relocations, relocation to foreign countries, and duty-related separation from parents. In recent years, the most impactful experiences have been repeated wartime deployments of parents and of the deaths of parents during military service.

All branches of the military have increased their focus on preparing and supporting military families for a service member’s deployment to improve family coping. Military families composed of young parents and young children are at risk for child maltreatment in the context of repeated or prolonged deployments.

PARENTAL/SIBLING DEATH
Approximately 5-8% of U.S. children will experience parental death; rates are much higher in other parts of the world that are more directly affected by war, AIDS, and natural disasters. Anticipated deaths from chronic illness may place a significant strain on a family, with frequent bouts of illness, hospitalization, disruption of normal home life, absence of the ill parent, and perhaps more responsibilities placed on the child. Additional strains include changes in daily routines, financial pressures, and the need to cope with aggressive treatment options.

Children can and should continue to be involved with the sick parent or sibling, but they need to be prepared for what they will see in the home or hospital setting. The stresses that a child will face include visualizing the physical deterioration of the family member, helplessness, and emotional lability. Forewarning the child that the family member may demonstrate physical changes, such as appearing thinner or losing hair will help the child to adjust. These warnings, combined with simple yet specific explanations of the need for equipment, such as a nasogastric tube for nutrition, an oxygen mask, or a ventilator, will help lessen the child’s fear. Children should be honestly informed of what is happening, in language they can understand, allowing them choices, but with parental involvement in decision making. They should be encouraged, but not forced, to see their ill family member. Parents who are caring for a dying spouse or child may be too emotionally depleted to be able to tend to their healthy child’s needs or to continue regular routines. Children of a dying parent may suffer the loss of security and belief in the world as a safe place, and the surviving parent may be inclined to impose his or her own need for support and comfort onto the child. However, the well parent and caring relatives must keep in mind that children need to be allowed to remain children, with appropriate support and attention. Sudden unexpected deaths lead to more anxiety and fear, because there was no time for preparation and uncertainty as to explanations.

GRIEF AND BEREAVEMENT
Grief is a personal, emotional state of bereavement or an anticipated response to loss, such as a death. Common reactions include sadness, anger, guilt, fear, and at times, relief. The normality of these reactions needs to be emphasized. Most bereaved families remain socially connected and expect that life will return to some new, albeit different, sense of normalcy. The pain and suffering imposed by grief should never be automatically deemed “normal” and thus neglected or ignored. In uncomplicated grief reactions, the steadfast concern of the pediatrician can help promote the family’s sense of well-being. In more distressing reactions (such as those seen in traumatic grief of sudden deaths), the pediatrician may be a major, first-line force in helping children and families address their loss.

Participation in the care of a child with a life-threatening or terminal illness is a profound experience. Parents experience much anxiety and worry during the final stages of their child’s life. In 1 study at a children’s hospital, 45% of children dying from cancer died in the pediatric intensive care unit, and parents report that 89% of their children suffered “a lot” or “a great deal” during the last month of life. Physicians consistently underreport children’s symptoms in comparison to parents’ reports. Better ways are needed to provide for dying children, and to maintain honest and open communication, provide appropriate pain management, and meet the families’ wishes as to the preferred location of the child’s death, in some cases in their own home. Inclusion of multiple disciplines, such as hospice, clergy, nursing, pain service, child life specialists, and social work, often helps to fully support families during this difficult experience.
The practice of withholding information from children and parents regarding a child's diagnosis and prognosis has generally been abandoned because physicians have learned that protecting parents and patients from the seriousness of their child's condition does not alleviate concerns and anxieties. Even very young children may have a real understanding of their illness. Children who have serious diseases and are undergoing aggressive treatment and medication regimens, but are told by their parents that they are okay, are not reassured by their parents. These children understand that something serious is happening to them, and they are often forced to suffer in silence and isolation because the message they have been given by their parents is to not discuss it and to maintain a cheerful demeanor. Children have the right to know their diagnosis and should be informed early in their treatment. The content and depth of the discussion needs to be tailored to the child's personality and developmental level of understanding. Parents have choices as to how to orchestrate the disclosure. Parents may want to be the ones to inform the child themselves, may choose for the pediatric healthcare provider to do so, or may do it in partnership with the pediatrician.

A death, especially the death of a family member, is the most difficult loss for a child. Many changes in normal patterns of functioning may occur, including loss of love and support from the deceased family member, a change in income, the possible need to relocate, less emotional support from surviving family members, altering of routines, and a possible change in status from sibling to only child. Relationships between family members may become strained, and children may blame themselves or other family members for the death of a parent or sibling. Bereaved children may exhibit many of the emotions discussed earlier as a result of the loss, in addition to behaviors of withdrawal into their own world, sleep disturbances, nightmares, and symptoms such as headache, abdominal pains, or possibly similar to those of the family member who has died. Children 3-5 yr of age who have experienced a family bereavement may show regressive behaviors such as bed-wetting and thumb sucking. School-age children may exhibit nonspecific symptoms, such as headache, abdominal pain, chest pain, fatigue, and lack of energy. Children and adolescents may also demonstrate enhanced anxiety should these symptoms resemble those of the family member who died. The presence of secure and stable adults who can meet the child's needs and who permit discussion about the loss is most important in helping a child to grieve. The pediatrician should help the family understand this necessary presence and encourage the protective functioning of the family unit. More frequent visits to the healthcare professional may be necessary to address these symptoms and provide reassurance when appropriate.

Death, separation, and loss as a result of natural catastrophes and human-made disasters have become increasingly common events in children's lives. Exposure to such disasters occurs either directly or indirectly, where the event is experienced through the media. Examples of indirect exposure include televised scenes of earthquakes, hurricanes, tsunamis, tornadoes and the terrorist attacks at the Boston Marathon in 2013 and in New York on September 11, 2001, with the subsequent news stories about anthrax and heightened states of alert. Children who experience personal loss in disasters tend to watch more television coverage than children who do not. Children without a personal loss watch as a way of participating in the event and may thus experience repetitive exposure to traumatic scenes and stories. The loss and devastation for a child who personally lives through a disaster is significant; the effect of the simultaneous occurrence of disaster and personal loss complicates the bereavement process as grief reactions become interwoven with posttraumatic stress symptoms (see Chapter 25). After a death that occurs as a result of aggressive or traumatic circumstances, access to expert help may be required. Under conditions of threat and fear, children seek proximity to safe, stable, protective figures.

It is important for parents to grieve with their children. Some parents want to protect their children from their grief, so they put on an outwardly brave front or do not talk about the deceased family member. Instead of the desired protective effect, the child receives the message that demonstrating grief or talking about death is wrong, leading the child to feel isolated, to grieve privately, or to delay grieving. The child may also conclude that the parents didn't really care about the deceased because they have forgotten the deceased so easily or demonstrate no emotion. The parents' efforts to avoid talking about the death may cause the parents to isolate themselves from their children at a time when the children most need them. Children need to know that their parents love them and will continue to protect them. Children need opportunities to talk about their relative's death and associated memories. A surviving sibling may feel guilty simply because he or she survived, especially if the death was the result of an accident that involved both children. Siblings' grief, especially when compounded by feelings of guilt, may be manifested by regressive behavior or anger. Parents should be informed of this possibility and encouraged to discuss the possibility with their children.

**DEVELOPMENTAL PERSPECTIVE**

Children's responses to death reflect the family's current culture, their past heritage, experiences, and the sociopolitical environment. Personal experience with terminal illness and dying may also facilitate children's comprehension of death and familiarity with mourning. Developmental differences in children's efforts to make sense of and master the concept and reality of death do exist and profoundly influence their grief reactions.

Children younger than 3 yr of age have little or no understanding of the concept of death. Despair, separation anxiety, and detachment may occur at the withdrawal of nurturing caretakers. Young children may respond in reaction to observing distress in others, such as a parent or sibling who is crying, withdrawn, or angry. Young children also express signs and symptoms of grief in their emotional states, such as irritability or lethargy, and in severe cases, mutism. If the reaction is severe, failure to thrive may occur.

**Preschool children** are in the preoperational cognitive stage, in which communication takes place through play and fantasy (see Chapter 6). They do not show well-established cause-and-effect reasoning. They feel that death is reversible, analogous to someone going away. In attempts to master the finality and permanence of death, preschoolers frequently ask unrelenting, repeated questions about when the person who died will be returning. This makes it difficult for parents, who may become frustrated because they don't understand why the child keeps asking and do not like the constant reminders of the person's death. The primary care provider has a very important role in helping families understand the child's struggle to comprehend death. Preschool children typically express magical explanations of death events, sometimes resulting in guilt and self-blame (“He died because I wouldn't play with him.” “She died because I was mad at her.”). Some children have these thoughts, but do not express them verbally because of embarrassment or guilt. Parents and primary care providers need to be aware of magical thinking and must reassure preschool children that their thoughts had nothing to do with the outcome. Children of this age are often frightened by prolonged, powerful expressions of grief by others. Children conceptualize events in the context of their own experiential reality, and therefore consider death in terms of sleep, separation, and injury. Young children express grief intermittently and show marked affective shifts over brief periods. Regression, accompanied by longing, sadness, and anger, may accompany grief.

Younger school-age children think concretely, recognize that death is irreversible, but believe it will not happen to them or affect them, and begin to understand biologic processes of the human body (“You'll die if your body stops working”). Information gathered from the media, peers, and parents forms lasting impressions. Consequently, they may ask candid questions about death that adults will have difficulty addressing (“He must have been blown to pieces, huh?”).

Children 9 yr of age and older do understand that death is irreversible and that it may involve them or their families. These children tend to experience more anxiety, overt symptoms of depression, and somatic complaints than do younger children. School-aged children are often left with anger focused on the loved one, those who could not save the deceased, or those presumed responsible for the death. Contact with
the pediatrician may provide great reassurance, especially for the child with somatic symptoms, and particularly when the death followed a medical illness. School and learning problems may also occur, and these reactions are often linked to difficulty concentrating or preoccupation with the death. Close collaboration with the child’s school may provide important diagnostic information and offer opportunities to mobilize intervention or support.

At 12-14 yr of age, children begin to use symbolic thinking, reason abstractly, and analyze hypothetical, or “what if” scenarios systematically. Death and the end of life become concepts, rather than events. Teenagers are often ambivalent about dependence and independence and may withdraw emotionally from surviving family members, only to mourn in isolation. Adolescents begin to understand complex physiologic systems in relationship to death. Since they are often egocentric, they may be more concerned about the impact of the death on themselves than about the deceased or other family members. Fascination with dramatic, sensational, or romantic death sometimes occurs and may find expression in copycat behavior, such as cluster suicides, as well as competitive behavior to forge emotional links to the deceased person (“He was my best friend.”). Somatic expression of grief may revolve around highly complex syndromes (eating disorders or conversion reactions) as well as symptoms limited to the more immediate perceptions, as with younger children (stomachaches). Quality of life takes on meaning, and the teenager develops a focus on the future. Depression, resentment, mood swings, rage, and risk-taking behaviors can emerge as the adolescent seeks answers to questions of values, safety, evil, and fairness. Alternately, the adolescent may seek philosophical or spiritual explanations ("being at peace") to ease their sense of loss. The death of a peer may be especially traumatic.

Families often struggle with how to inform their children of the death of a family member. The answer depends on the child’s developmental level. It is best to avoid misleading euphemisms and metaphors. A child who is told that the relative who died “went to sleep” may become frightened of falling asleep, resulting in sleep problems or nightmares. Children can be told that the person is “no longer living” or “no longer moving or feeling.” Using examples of pets that have died sometimes can help children gain a more realistic idea of the meaning of death. Parents who have religious beliefs may comfort their children with explanations, such as “Your sister’s soul is in heaven” or “Grandfather is now with God,” provided those beliefs are honestly held. If these are not religious beliefs that the parents share, children will sense the insincerity and experience anxiety rather than the hoped-for reassurance. Children’s books about death can provide an important source of information, and when read together, these books may help the parent to find the right words, while addressing the child’s needs.

**ROLE OF THE PEDIATRICIAN IN GRIEF**

The pediatrician has an important role in assisting grieving families, because the death of a child has become an uncommon experience in our society. The pediatric healthcare provider who has had a longitudinal relationship with the family will be an important source of support in the disclosure of bad news and critical decision making, during both the dying process and the bereavement period.

The involvement of the healthcare provider may include being present at the time the diagnosis is disclosed, at the hospital or home at the time of death, being available to the family by phone during the bereavement period, sending a sympathy card, attending the funeral, and/or scheduling a follow-up visit. Attendance at the funeral sends a strong message that the family and their child are important, respected by the healthcare provider, and can also help the pediatric healthcare provider to grieve and reach personal closure about the death. A family meeting 1-3 mo later may be helpful because parents may not be able to formulate their questions at the time of death. This meeting allows the family time to ask questions, share concerns, and review autopsy findings (if one was performed), and allows the healthcare provider to determine how the parents and family are adjusting to the death.

Instead of leaving the family feeling abandoned by a healthcare system that they have counted on, this visit allows them to have continued support. This is even more important when the healthcare provider will be continuing to provide care for surviving siblings. The visit can be used to determine how the mourning process is progressing, detect evidence of marital discord, and evaluate how well surviving siblings are coping. This is also an opportunity to evaluate whether referrals to support groups or mental health providers may be of benefit. Continuing to recognize the child who has died is important. Families appreciate the receipt of a card on their child’s birthday or the anniversary of their child’s death.

The healthcare provider needs to be an educator about disease, death, and grief. The pediatrician can offer a safe environment for the family to talk about painful emotions, express fears, and share memories. By giving families permission to talk and modeling how to address children’s concerns, the pediatrician demystifies death. Parents often request practical help. The healthcare provider can offer families resources, such as literature (both fiction and nonfiction), referrals to therapeutic services, and tools to help them learn about illness, loss, and grief. In this way, the physician reinforces the sense that other people understand what they are going through and helps to normalize their distressing emotions. The pediatrician can also facilitate and demystify the grief process by sharing basic tenets of grief therapy. There is no single right or wrong way to grieve. Everyone grieves differently; mothers may grieve differently than fathers, and children mourn differently than adults. Helping family members to respect these differences and reach out to support each other is critical. Grief is not something to “get over,” but a lifelong process of adapting, readjusting, and reconnecting.

Parents may need help in knowing what constitutes normal grieving. Hearing, seeing, or feeling their child’s presence may be a normal response. Vivid memories or dreams may occur. The pediatrician can help parents to learn that, although their pain and sadness may seem intolerable, other parents have survived similar experiences, and their pain will lessen over time.

Pediatricians are often asked whether children should attend the funeral of a parent or sibling. These rituals allow the family to begin their mourning process. Children older than 4 yr of age should be given a choice. If the child chooses to attend, the child should have a designated, trusted adult, who is not part of the immediate family, stay with the child, offer comfort, and be willing to leave with the child if the experience proves to be overwhelming. If the child chooses not to attend, the child should be offered additional opportunities to share in a ritual, go to the cemetery to view the grave, tell stories about the deceased, or obtain a keepsake object from the deceased family member as a remembrance.

In the era of regionalized tertiary care medicine, the primary care provider and medical home staff may not be informed when one of their patients dies in the hospital. Yet, this communication is critically important. Families assume their pediatrician has been notified, and they often feel hurt when they don’t receive some symbol of condolence. Because of their longitudinal relationship with the family, primary care providers may offer much needed support. There are practical issues, such as the need to cancel previously made appointments and the need to alert office and nursing staff so that they are prepared should the family return for a follow-up visit or for ongoing health maintenance care with the surviving siblings. Even minor illnesses in the surviving siblings may frighten children. Parents may contribute to this anxiety because their inability to protect the child who has died may leave them with a sense of guilt or helplessness. They may seek medical attention sooner or may be hypervigilant in the care of the siblings because of guilt over the other child’s death, concern about their judgment, or the need for continued reassurance. A visit to the pediatrician can do a lot to allay their fears.

Clinicians must remain vigilant for risk factors in each family member and in the family unit as a whole. Primary care providers, who care for families over time, know bereft patients’ premorbid functioning and can identify those at current or future risk for physical and psychiatric morbidity. Providers must focus on symptoms that interfere with a patient’s normal activities and compromise a child’s attainment of developmental tasks. Symptom duration, intensity, and severity, in context with the family’s culture, can help identify
complicated grief reactions in need of therapeutic attention. Descriptive words, such as “unrelenting,” “intense,” “intrusive,” or “prolonged,” should raise concern. Total absence of signs of mourning, specifically, an inability to discuss the loss or express sadness, also suggests potential problems.

No specific sign, symptom, or cluster of behaviors identifies the child or family in need of help. Further assessment is indicated if the following occur: (1) persistent somatic or psychosomatic complaints of undetermined origin (headache, stomachache, eating and sleeping disorders, conversion symptoms, symptoms related to the deceased’s condition, hypochondriasis); (2) unusual circumstances of death or loss (sudden, violent, or traumatic death; inexplicable, unbelievable, or particularly senseless death; prolonged, complicated illness; unexpected separation); (3) school or work difficulties (declining grades or school performance, social withdrawal, aggression); (4) changes in home or family functioning (multiple family stresses, lack of social support, unavailable or ineffective functioning of caretakers, multiple disruptions in routines, lack of safety); (5) concerning psychologic factors (persistent guilt or blame, desire to die or talk of suicide, severe separation distress, disturbing hallucinations, self-abuse, risk-taking behaviors, symptoms of trauma such as hyperarousal or severe flashbacks, grief from previous or multiple deaths). Children who are intellectually impaired may require additional support.

TREATMENT
Suggesting interventions outside the natural support network of family and friends can often prove useful to grieving families. Bereavement counseling should be readily offered if needed or requested by the family. Interventions that enhance or promote attachments and security, as well as give the family a means of expressing and understanding death, help to reduce the likelihood of future or prolonged disturbance, especially in children. Collaboration between pediatric and mental health professionals can help determine the timing and appropriateness of services.

Interventions for children and families who are struggling to cope with a loss in the community include gestures such as sending a card or offering food to the relatives of the deceased and teaching children the etiquette of behaviors and rituals around bereavement and mutual support. Performing community service or joining charitable organizations, such as fund-raising in memory of the deceased, may be useful. In the wake of a disaster, parents and older siblings can give blood or volunteer in search and recovery efforts. When a loss does not involve an actual death (e.g., parental divorce or geographic relocation), empowering the child to join or start a “divorced kids’ club” in school or planning a “new kids in town” party may help. Participating in a constructive activity helps move the family away from a sense of helplessness and hopelessness and helps them to find meaning in their loss.

Psychotherapeutic services may benefit the entire family or individual members. Many support or self-help groups focus on specific types of losses (sudden infant death syndrome, suicide, widow/widowers, or AIDS) and provide an opportunity to talk with other people who have experienced similar losses. Family, couple, sibling or individual counseling may be useful, depending on the nature of the residual coping issues. Combinations of approaches may work well for children or parents with evolving needs. A child may participate in family therapy to deal with the loss of a sibling and use individual treatment to address issues of personal ambivalence and guilt related to the death.

The question of pharmacologic intervention for grief reactions often arises. Explaining that medication does not cure grief and often does not reduce the intensity of some symptoms (separation distress) can help. Although medication can blunt reactions, the psychologic work of grieving still must occur. The pediatrician must consider the patient’s premorbid psychiatric vulnerability, current level of functioning, other available supports, and the use of additional therapeutic interventions. Medication, as a first line of defense, rarely proves useful in normal or uncomplicated grief reactions. In certain situations (severe sleep disruption, incapacitating anxiety, or intense hyperarousal), use of an anxiolytic or antidepressant medication for symptom relief and to provide the patient with the emotional energy to mourn may help. Medication used in conjunction with some form of psychotherapy, and in consultation with a psychopharmacologist, has optimal results.

Children who are refugees and may have experienced war, violence, or personal torture, while often resilient, may experience post-traumatic stress disorder if exposures were severe or repeated. Sequelae such as depression, anxiety, and grief need to be addressed, and mental health therapy is indicated. Cognitive behavioral treatment, use of journaling and narratives to bear witness to the experiences, and use of translators may be essential.

SPIRITUAL ISSUES
Responding to patients’ and families’ spiritual beliefs can help in comforting them during family tragedies. Offering to call members of pastoral care teams or their own spiritual leader can be a real support to them and aid in decision-making. Families have found it important to have their beliefs and their need for hope acknowledged in end-of-life care. The majority of patients report welcoming discussions on spirituality, which may help individual patients cope with illness, disease, dying, and death. In addressing spirituality, physicians need to follow certain guidelines, including maintaining respect for the patient’s beliefs, following the patient’s lead in exploring how spirituality affects the patient’s decision making, acknowledging the limits of their own expertise and role in spirituality, and maintaining their own integrity by not saying or doing anything that violates their own spiritual or religious views. Healthcare providers should not impose their own religious or antireligious beliefs on patients, but rather should listen respectfully to their patients. By responding to spiritual needs, physicians may better aid their patients and families in end-of-life care and bereavement and take on the role of healers.

Bibliography is available at Expert Consult.
Chapter 18   Loss, Separation, and Bereavement

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Sleep regulation is also referred to as the 2-process sleep system because it requires the simultaneous operation of 2 basic, highly coupled processes that govern sleep and wakefulness. The homoeostatic process (“Process S”), regulates the length and depth of sleep, and may be related to the accumulation of adenosine and other sleep-promoting chemicals (“somnogens”), such as cytokines, during prolonged periods of wakefulness. This sleep pressure appears to build more quickly in infants and young children, thus limiting the duration that wakefulness can be sustained during the day and necessitating periods of daytime sleep (i.e., naps). The endogenous circadian rhythms (“Process C”), influence the internal organization of sleep and timing and duration of daily sleep–wake cycles, and govern predictable patterns of alertness throughout the 24 hr day. The “master circadian clock” that controls sleep–wake patterns, of which melatonin secretion is the principal biomarker, is located in the suprachiasmatic nucleus in the ventral hypothalamus. The “circadian clocks” govern the timing of multiple other physiologic systems in the body (e.g., cardiovascular reactivity, hormone levels, renal and pulmonary functions). Because the human circadian clock is actually slightly longer than 24 hr, intrinsic circadian rhythms must be synchronized or “entrained” to the 24 hr day cycle by environmental cues called zeitgebers. The dark–light cycle is the most powerful of the zeitgebers; light signals are transmitted to the suprachiasmatic nucleus via the circadian photoreceptor system within the retina (functionally and anatomically separate from the visual system), which switch the body’s production of the hormone melatonin off.
Part II Growth, Development, and Behavior

1. There is a gradual decline in the average 24 hr sleep duration from infancy through adolescence, which involves a decrease in both diurnal and nocturnal sleep amounts. The decline in daytime sleep (scheduled napping) results in termination of naps typically by around 5 yr of age. There is also a gradual continued decrease in nocturnal sleep amounts into late adolescence; however, the typical adolescent still requires 9-9.25 hr of sleep per night.

2. There are significant consequences of the failure to meet basic sleep needs, termed insufficient/inadequate sleep or sleep loss. Sufficient sleep is a biologic imperative, necessary for optimal functioning and apparently for life. Slow-wave sleep (SWS) (i.e., N3, delta, or deep sleep) appears to be the most restorative form of sleep; it is entered relatively quickly after sleep onset, is preserved in the face of reduced total sleep time, and it increases (rebounds) after a night of restricted sleep. Rapid eye movement (REM) sleep (Stage R or “dream” sleep) appears to be involved in (1) completing vital cognitive functions, such as the consolidation of memory; (2) promoting the plasticity of the central nervous system (CNS); and (3) protecting the brain from injury. Sufficient amounts of both of these sleep stages are necessary for optimal cognitive functioning. Partial sleep loss (sleep restriction) on a chronic basis accumulates in what is termed a sleep debt and produces deficits equivalent to those seen under conditions of total sleep deprivation. If the sleep debt becomes large enough and is not voluntarily repaid by obtaining sufficient recovery sleep, the body may respond by overriding voluntary control of wakefulness. This results in periods of decreased alertness, dozing off, and unplanned napping, recognized as excessive daytime sleepiness. The sleep-restricted individual may also experience very brief (several seconds) repeated daytime microsleeps of which the individual may be completely unaware, but which, nonetheless, may result in significant lapses in attention and vigilance. There is also a relationship between the amount of sleep restriction and performance on cognitive tasks, particularly those requiring sustained attention and higher level cognitive functions (executive functions), with a decay in performance correlating with declines in sleep amounts.

Both insufficient quantity and poor quality of sleep in children and adolescents usually result in excessive daytime sleepiness and decreased daytime alertness levels. Sleepiness in children may be recognizable as drowsiness, yawning, and other classic “sleepy behaviors,” but can also be manifested as mood disturbance, including complaints of moodiness, irritability, emotional lability, depression, and anger; fatigue and daytime lethargy, including increased somatic complaints (headaches, muscle aches); cognitive impairment, including problems with memory, attention, concentration, decision making, and problem solving; daytime behavior problems, including hyperactivity, impulsivity, and noncompliance; and academic problems, including chronic tardiness related to insufficient sleep and school failure resulting from chronic daytime sleepiness.

To evaluate sleep problems, it is important to have an understanding of what constitutes “normal” sleep in children and adolescents. Sleep disturbances, as well as many characteristics of sleep itself, have some distinctly different features in children from sleep and sleep disorders in adults. Changes in sleep architecture and the evolution of sleep patterns and behaviors reflect the physiologic/chronobiologic, developmental, and social/environmental changes that are occurring across childhood. These trends may be summarized as the gradual assumption of more adult sleep patterns as children mature:

1. Sleep is the primary activity of the brain during early development; for example, by age 2 yr, the average child has spent ~9500 hr (13 months) asleep compared to 8000 hr awake, and between 2 and 5 yr, the time asleep is equal to the time awake. 

2. There is a gradual decline in the average 24 hr sleep duration from infancy through adolescence, which involves a decrease in both diurnal and nocturnal sleep amounts. The decline in daytime sleep (scheduled napping) results in termination of naps typically by around 5 yr of age. There is also a gradual continued decrease in nocturnal sleep amounts into late adolescence; however, the typical adolescent still requires 9-9.25 hr of sleep per night.

3. There is also a decline in the relative percentage of REM sleep from birth (50% of sleep) through early childhood into adulthood (25-30%), and a similar initial predominance of SWS that peaks in early childhood, drops off abruptly after puberty (40-60% decline), and then further decreases over the life span. This SWS preponderance in early life has clinical significance; for example, the high prevalence of partial arousal parasomnias (sleepwalking and sleep terrors) in preschool and early school-age children is related to the relative increased percentage of SWS in this age group.

4. The within-sleep ultradian cycle lengths from about 50 minutes in the term infant to 90-110 minutes in the school-age child. This, again, has clinical significance in that there is typically a brief arousal or awakening during the night at the termination of each ultradian cycle. As the length of the cycles increase, there is a concomitant decrease in the number of these end-of-cycle arousals (“night wakings”).

5. A gradual shift in the circadian sleep–wake rhythm to a delayed (later) sleep onset and offset time, linked to pubertal stage rather than chronological age, begins in middle childhood and accelerates in early to mid-adolescence. This biologic phenomenon often coincides with environmental factors, which further delay bedtime and advance wake time and result in insufficient sleep duration, including exposure to electronic “screens” (i.e., television and computer) in the evening, social networking, academic and extracurricular demands, and early (before 8 AM) high school start times.

6. Increasing irregularity of sleep–wake patterns is typically observed across childhood into adolescence; this is characterized by increasingly larger discrepancies between school night and non–school night bedtimes and wake times, and increased “weekend oversleep” in an attempt to compensate for chronic weekday sleep insufficiency. This practice not only fails to adequately address performance deficits associated with insufficient sleep on school nights, but further exacerbates the normal adolescent phase delay and results in additional circadian disruption (analogous to that experienced by shift workers).

Table 19-1 lists normal developmental changes in children's sleep.

COMMON SLEEP DISORDERS

Childhood sleep problems may be conceptualized as resulting from either inadequate duration of sleep for age and sleep needs (insufficient sleep quantity) or disruption and fragmentation of sleep (poor sleep quality) as a result of frequent, repetitive, and brief arousals during sleep. Less common but important causes of sleep disturbance in childhood involve inappropriate timing of the sleep period (as occurs in circadian rhythm disturbances), or primary disorders of excessive daytime sleepiness (central hypersomnias such as narcolepsy). Insufficient sleep is usually the result of difficulty initiating (delayed sleep onset) and/or maintaining sleep (prolonged night wakings), but, especially in older children and adolescents, may also represent a conscious lifestyle decision to sacrifice sleep in favor of competing priorities, such as homework and social activities. The underlying causes of sleep onset delay/prolonged night wakings or sleep fragmentation may, in turn, be related to primarily behavioral factors (e.g., bedtime resistance resulting in shortened sleep duration) and/or medical causes (e.g., obstructive sleep apnea causing frequent, brief arousals). Certain pediatric populations are relatively more vulnerable to acute or chronic sleep problems. These include children with medical problems, including chronic illnesses or pain conditions, such as cystic fibrosis, asthma, and rheumatoid arthritis, and acute illnesses, such as otitis media; children taking medications or ingesting substances with...
stimulant (e.g., psychostimulants, caffeine), sleep-disrupting (e.g., corticosteroids), or daytime-sedating (some anticonvulsants, α-agonists) properties; hospitalized children; and children with a variety of psychiatric disorders, including attention-deficit/hyperactivity disorder (ADHD), depression, bipolar disorder, and anxiety disorders. Children with neurodevelopmental disorders such as blindness, mental retardation, some chromosomal syndromes (e.g., Smith-Magenis, fragile X), and autism spectrum disorders have especially high rates of sleep disturbances for a wide variety of reasons. They may be on sleep-disrupting medications, they are often more prone to nocturnal seizures, they may be less easily entrained by environmental cues and thus more vulnerable to circadian disruption, and are more likely to have

### Table 19-1 Normal Developmental Changes in Children’s Sleep

<table>
<thead>
<tr>
<th>AGE CATEGORY</th>
<th>SLEEP DURATION AND SLEEP PATTERNS</th>
<th>ADDITIONAL SLEEP ISSUES</th>
<th>SLEEP DISORDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn (0-2 mo)</td>
<td>Total sleep: 10-19 hr per 24 hr (average = 13-14.5 hr), may be higher in premature babies Bottlefed babies generally sleep for longer periods (2-5 hr bouts) than breastfed babies (1-3 hr) Sleep periods are separated by 1-2 hr awake No established nocturnal–diurnal pattern in the 1st few wk; sleep is evenly distributed throughout the day and night, averaging 8.5 hr at night and 5.75 hr during the day</td>
<td>The American Academy of Pediatrics issued a formal recommendation in 2005 advocating against bed sharing in the 1st yr of life, instead encouraging proximate but separate sleeping surfaces for mother and infant. Safe sleep practices for infants: • Place the baby on his or her back to sleep at night and during nap times • Place the baby on a firm mattress with a well-fitting sheet in a safety-approved crib • Do not use pillows or comforters • Cribs should not have corner posts over ¾ in high or decorative cutouts • Make sure the baby’s face and head stay uncovered and clear of blankets and other coverings during sleep</td>
<td>Most sleep issues that are perceived as problematic at this stage represent a discrepancy between parental expectations and developmentally appropriate sleep behaviors Newborns who are noted by parents to be extremely fussy and persistently difficult to console are more likely to have underlying medical issues, such as colic, gastroesophageal reflux, and formula intolerance</td>
</tr>
<tr>
<td>Infant (2-12 mo)</td>
<td>Total sleep: average is 12-13 hr (note that there is great individual variability in sleep times during infancy) Nighttime: average is 9-10 hr Naps: average is 3-4 hr</td>
<td>Sleep regulation or self-soothing involves the infant’s ability to negotiate the sleep–wake transition, both at sleep onset and following normal awakenings throughout the night. The capacity to self-soothe begins to develop in the 1st 12 wk of life, and is a reflection of both neurodevelopmental maturation and learning Sleep consolidation, or “sleeping through the night,” is usually defined by parents as a continuous sleep episode without the need for parental intervention (e.g., feeding, soothing) from the child’s bedtime through the early morning. Infants develop the ability to consolidate sleep between 6 wk and 3 mo</td>
<td>Behavioral insomnia of childhood; sleep onset association type Sleep-related rhythmic movements (head banging, body rocking)</td>
</tr>
<tr>
<td>Toddler (1-3 yr)</td>
<td>Total sleep: average is 11-13 hr Nighttime: average is 9.5-10.5 hr Naps: average is 2-3 hr; decrease from 2 naps to 1 at average age of 18 mo</td>
<td>Cognitive, motor, social, language developmental issues impact on sleep Nighttime fears develop; transitional objects, bedtime routines important</td>
<td>Behavioral insomnia of childhood, sleep onset association type Behavioral insomnia of childhood, limit setting type</td>
</tr>
<tr>
<td>Preschool (3-5 yr)</td>
<td>Nighttime: average is 9-10 hr Naps: decrease from 2 naps to 1 at average age of 5 yr olds nap Overall, 26% of 4 yr olds and just 15% of 5 yr olds nap</td>
<td>Persistent cosleeping tends to be highly associated with sleep problems in this age group Sleep problems may become chronic</td>
<td>Behavioral insomnia of childhood, limit setting type Sleepwalking Sleep terrors Nighttime fears/nightmares Obstructive sleep apnea</td>
</tr>
<tr>
<td>Middle childhood (6-12 hr)</td>
<td>9-11 hr</td>
<td>School and behavior problems may be related to sleep problems Media and electronics, such as television, computer, video games, and the Internet increasingly compete for sleep time Irregularity of sleep–wake schedules reflects increasing discrepancy between school and non-school night bedtimes and wake times</td>
<td>Nightmares Obstructive sleep apnea Insufficient sleep</td>
</tr>
<tr>
<td>Adolescence (&gt;12 yr)</td>
<td>Average sleep duration 7.7-7.5 hr; only 20% of adolescents overall get the recommended 9-9.25 hr of sleep Later bedtimes; increased discrepancy sleep patterns weekdays/weekends</td>
<td>Puberty-mediated phase delay (later sleep onset and wake times), relative to sleep-wake cycles in middle childhood Earlier required wake times Environmental competing priorities for sleep</td>
<td>Insufficient sleep Delayed sleep phase disorder Narcolepsy Restless legs syndrome/periodic limb movement disorder</td>
</tr>
</tbody>
</table>
comorbid psychiatric and behavioral conditions which that further predispose them to disrupted sleep.

Insomnia of Childhood
Insomnia is difficulty initiating and/or maintaining sleep that occurs despite age-appropriate time and opportunity for sleep and results in some degree of impairment in daytime functioning for the child and/or family (ranging from fatigue, irritability, lack of energy, and mild cognitive impairment to effects on mood, school performance, and quality of life). Insomnia may be of a short-term and transient nature (usually related to an acute event), or may be characterized as long-term and chronic. Insomnia is a set of symptoms with a large number of possible etiologies (e.g., pain, medication, medical and psychiatric conditions, learned behaviors). Insomnia, like many behavioral issues in children, is often primarily defined by parental concerns rather than by objective criteria, and therefore should be viewed in the context of family (i.e., maternal depression, stress), child (i.e., temperament, developmental level), and environmental (i.e., cultural practices, sleeping space) considerations.

One of the most common presentations of insomnia found in infants and toddlers is the sleep-onset association type. In this situation, the child learns to fall asleep only under certain conditions or associations, which typically require parental presence, such as being rocked or fed, and does not develop the ability to self-soothe. During the night, when the child experiences the type of brief arousal that normally occurs at the end of an ultradian sleep cycle or awakens for other reasons, the child is not able to get back to sleep without those same associations being present. The infant then “signals” the parent by crying (or coming into the parents’ bedroom, if the child is ambulatory) until the necessary associations are provided. The presenting complaint is typically one of prolonged night waking resulting in insufficient sleep (for both child and parent).

Management of night wakeings should include establishment of a set sleep schedule and bedtime routine, and implementation of a behavioral program. The treatment approach typically involves a program of rapid withdrawal (extinction) or more gradual withdrawal (graduated extinction) of parental assistance at sleep onset and during the night. Extinction (“cry it out”) involves putting the child to bed at a designated bedtime, “drowsy but awake” to maximize sleep propensity, and then systematically ignoring any protests by the child until a set time the next morning. Although it has considerable empirical support, extinction is often not an acceptable choice for families. Graduated extinction involves gradually weaning the child from dependence on parental presence; typically, the parent leaves the room at “lights out” and then returns or “checks” periodically at fixed or successively longer intervals during the sleep–wake transition to provide brief reassurance until the child falls asleep. The exact time interval between checks is generally determined by the parents’ tolerance for crying and the child’s temperament. The goal is to allow the infant or child to develop skills in self-soothing during the night, as well as at bedtime. In older infants, the introduction of more appropriate sleep associations that will be readily available to the child during the night (transitional objects, such as a blanket or toy), in addition to positive reinforcement (i.e., stickers for remaining in bed), is often beneficial. If the child has become habituated to awaken for nighttime feedings (learned hunger), then these feedings should be slowly eliminated. Parents must be consistent in applying behavioral programs to avoid inadvertent, intermittent reinforcement of night wakeings; they should also be forewarned that crying behavior often temporarily escalates at the beginning of treatment (postextinction burst).

Bedtime problems, including stalling and refusing to go to bed, are more common in preschool-age and older children. This type of insomnia is frequently related to inadequate limit setting and is often the result of parental difficulties in setting limits and managing behavior in general, and the inability or unwillingness to set consistent bedtime rules and enforce a regular bedtime in particular. The situation may be exacerbated by the child’s oppositional behavior. In some cases the child’s resistance at bedtime is the result of an underlying problem in falling asleep that is caused by other factors (medical conditions, such as asthma or medication use; a sleep disorder, such as restless legs syndrome; or anxiety) or a mismatch between the child’s intrinsic circadian rhythm (“night owl”) and parental expectations regarding an “appropriate” bedtime.

Successful treatment of limit-setting sleep problems generally involves a combination of parent education regarding appropriate limit setting, decreased parental attention for bedtime-delaying behavior, establishment of bedtime routines, and positive reinforcement (sticker charts) for appropriate behavior at bedtime; other behavioral management strategies that have empirical support include bedtime fading (temporarily setting the bedtime closer to the actual sleep onset time and then gradually advancing the bedtime to an earlier target bedtime). Older children may benefit from being taught relaxation techniques to help themselves fall asleep more readily. Following the principles of healthy sleep practices for children is essential (Table 19-2).

When the insomnia is not primarily a result of parent behavior or secondary to another sleep disturbance, or to a psychiatric or medical problem, it is often referred to as psychophysiological or primary or learned insomnia. Primary insomnia occurs largely in adolescents and is characterized by a combination of learned sleep-preventing associations and heightened psychophysiological arousal resulting in a complaint of sleeplessness and decreased daytime functioning. A hallmark of primary insomnia is excessive worry about sleep and an exaggerated concern of the potential daytime consequences. The psychophysiological arousal can be in the form of cognitive hypervigilance, such as “racing” thoughts; in many individuals with insomnia an increased baseline level of arousal is further intensified by this secondary anxiety about sleeplessness. Treatment usually involves educating the adolescent about the principles of healthy sleep practices (Table 19-3), institution of a consistent sleep–wake schedule, avoidance of daytime napping, instructions to use the bed for sleep only and to get out of bed if unable to fall asleep (stimulus control), restricting time in bed to the actual time asleep (sleep restriction), addressing maladaptive cognitions about sleep, and teaching relaxation techniques to reduce anxiety. Hypnotic medications are rarely needed.

Obstructive Sleep Apnea
Sleep-disordered breathing (SDB) in children encompasses a broad spectrum of respiratory disorders that occur exclusively in or are

<table>
<thead>
<tr>
<th>Table 19-2</th>
<th>Basic Principles of Healthy Sleep for Children</th>
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<tbody>
<tr>
<td>1. Have a set bedtime and bedtime routine for your child.</td>
<td></td>
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<tr>
<td>2. Bedtime and wake-up time should be about the same time on school nights and non-school nights. There should not be more than about an hour difference from one day to another.</td>
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<tr>
<td>3. Make the hour before bed shared quiet time. Avoid high-energy activities, such as rough play, and stimulating activities, such as watching television or playing computer games, just before bed.</td>
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<tr>
<td>4. Don’t send your child to bed hungry. A light snack (such as milk and cookies) before bed is a good idea. Heavy meals within an hour or 2 of bedtime, however, may interfere with sleep.</td>
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<tr>
<td>5. Avoid products containing caffeine for at least several hours before bedtime. These include caffeinated sodas, coffee, tea, and chocolate.</td>
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<tr>
<td>6. Make sure your child spends time outside every day, whenever possible, and is involved in regular exercise.</td>
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<tr>
<td>8. Keep your child’s bedroom at a comfortable temperature during the night (&lt;24°C [75°F]).</td>
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<tr>
<td>9. Don’t use your child’s bedroom for time-out or punishment.</td>
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<tr>
<td>10. Keep the television set out of your child’s bedroom. Children can easily develop the bad habit of “needing” the television to fall asleep. It’s also much more difficult to control your child’s viewing if the set is in the bedroom.</td>
<td></td>
</tr>
</tbody>
</table>
Basic Principles of Healthy Sleep for Adolescents

1. Wake up and go to bed at the same time every night. Bedtime and wake-up time should not differ from school to non-school nights by more than approximately 1 hr.

2. Avoid sleeping in on weekends to “catch up” on sleep. This makes it more likely that you will have problems falling asleep.

3. If you take naps, they should be short (no more than 1 hr) and scheduled in the early to mid afternoon. However, if you have a problem with falling asleep at night, napping during the day may make it worse and should be avoided.

4. Spend time outside every day. Exposure to sunlight helps to keep your body’s internal clock on track.

5. Exercise regularly. Exercise may help you fall asleep and sleep more deeply.

6. Use your bed for sleeping only. Don’t study, read, listen to music, watch television, etc., on your bed.

7. Make the 30-60 minutes before a quiet or wind-down time. Relaxing, calm, enjoyable activities, such as reading a book or listening to calm music, help your body and mind slow down enough to let you get to sleep. Don’t study, watch exciting or scary movies, exercise, or get involved in “energizing” activities just before bed.

8. Eat regular meals and don’t go to bed hungry. A light snack before bed is a good idea; eating a full meal in the hour before bed is not.

9. Avoid eating or drinking products containing caffeine from dinner time on. These include caffeinated sodas, coffee, tea, and chocolate.

10. Do not use alcohol. Alcohol disrupts sleep and may cause you to awaken throughout the night.

11. Smoking disturbs sleep. Don’t smoke at least 1 hr before bed (and preferably, not at all!).

12. Don’t use sleeping pills, melatonin, or other nonprescription sleep aids to help you sleep unless specifically recommended by your doctor. These can be dangerous, and the sleep problems often return when you stop taking the medicine.

Upper airway obstruction varies in degree and level (i.e., nose, nasopharynx/oropharynx, hypopharynx) and is most commonly caused by adenotonsillar hypertrophy, although tonsillar size does not necessarily correlate with degree of obstruction, especially in older children. Other causes of airway obstruction include allergies associated with chronic rhinitis/nasal obstruction; craniofacial abnormalities, including hypoplasia/displacement of the maxilla and mandible; gastroesophageal reflux with resulting pharyngeal reactive edema (see Chapter 323); nasal septal deviation (see Chapter 376); and velopharyngeal flap cleft palate repair. Reduced upper airway tone may result from neuromuscular diseases, including hypotonic cerebral palsy and muscular dystrophies (see Chapter 609), or hypothyroidism (see Chapter 565). Reduced central ventilatory drive may be present in some children with Arnold-Chiari malformation (see Chapter 418), rapid-onset obesity with hypothalamic dysfunction, hypventilation, and autonomic dysregulation, and meningocele (see Chapter 591). In other situations, the etiology is mixed; individuals with Down syndrome (see Chapter 81), by virtue of their facial anatomy, hypotonia, macrogllossia, and central adiposity, as well as the increased incidence of hypothyroidism, are at particularly high risk for OSA, with some estimates of as great as 70% prevalence.

Although many children with OSA are of normal weight, an increasing large percentage are overweight or obese, and many of these children are school-age and younger (see Chapter 47). There is a significant correlation between weight and SDB (e.g., habitual snoring, OSA, sleep-related hypventilation). Although adenotonsillar hypertrophy also plays an important etiologic role in overweight/obese children with OSA, mechanical factors related to an increase in the amount of adipose tissue in the throat (pharyngeal fat pads), neck (increased neck circumference), and chest wall and abdomen can create increased upper airway resistance, worsen gas exchange, and increased work of breathing, particularly in the supine position and during REM sleep. There may be a component of blunted central ventilatory drive in response to hypoxia/hypercapnia and hypventilation as well (see Chapter 418.3), particularly in children with morbid or syndrome-based (e.g., Prader-Willi) obesity. Overweight and obese children and adolescents are at a particularly high risk for metabolic and cardiovascular complications of SDB, such as insulin resistance and systemic hypertension; morbidly obese children are also at increased risk for postoperative complications as well as residual OSA following adenotonsillectomy.
Epidemiology

Overall prevalence of parent-reported snoring in the pediatric population is approximately 8%; “always” snoring is reported in 1.5-6%, and “often” snoring in 3-15%. When defined by parent-reported symptoms, the prevalence of OSA is 4-11%. The prevalence of pediatric OSA as documented by overnight sleep studies utilizing ventilatory monitoring procedures (e.g., in-lab polysomnography [PSG], home studies) is 1-4% overall, with a reported range of 0.1-1.3%. Prevalence is also affected by the demographic characteristics, such as age (increased prevalence between 2 and 8 yr), gender (more common in boys, especially after puberty), race/ethnicity (increased prevalence in African-American and Asian children), history of prematurity, and family history of OSA.

Pathogenesis

The upregulation of inflammatory pathways, as indicated by an increase in peripheral markers of inflammation such as C-reactive protein, appear to be linked to metabolic dysfunction (e.g., insulin resistance, dyslipidemia) in both obese and nonobese children with OSA. Both systemic inflammation and arousal-mediated increases in sympathetic autonomic nervous system activity with altered vaso-motor tone may be key contributors to increased cardiovascular risk in both adults and children with OSA. Mechanical stress on the upper airway induced by chronic snoring may also result in both local mucosal inflammation of adenotonsillar tissues and subsequent upregulation of inflammatory molecules, most notably leukotrienes. Another potential mechanism that may mediate cardiovascular sequelae in both adults and children with OSA is altered endothelial function.

One of the primary mechanisms by which OSA is believed to exert negative influences on cognitive function appears to involve repeated episodic arousals from sleep leading to sleep fragmentation and resulting sleepiness. An equally important role may be intermittent hypoxia that leads directly to systemic inflammatory vascular changes in the brain. Levels of inflammatory markers such as C-reactive protein and cytokine interleukin-6 are elevated in children with OSA and are also associated with cognitive dysfunctions.

Clinical Manifestations

The clinical manifestations of OSA may be divided into sleep-related and daytime symptoms. The most common nocturnal manifestations of OSA in children and adolescents are loud, frequent, and disruptive snoring, breathing pauses, choking or gasping arousals, restless sleep, and nocturnal diaphoresis. Many children who snore do not have OSA, but very few children with OSA do not snore. Children, like adults, tend to have more frequent and more severe obstructive events in REM sleep and when sleeping in the supine position. Children with OSA may adopt unusual sleeping positions, keeping their necks hyperextended to maintain airway patency. Frequent arousals associated with obstruction may result in nocturnal awakenings, but are more likely to cause fragmented sleep.

Daytime symptoms of OSA include mouth breathing and dry mouth, chronic nasal congestion/rhinorrhea, hoarseness, speaking, morning headaches, difficulty swallowing, and poor appetite. Children with OSA may have secondary enuresis, which has been postulated to result from the disruption of the normal nocturnal pattern of antidiuretic hormone or atrial natriuretic peptide secretion. Partial arousal parasomnias (sleepwalking and sleep terrors) may occur more frequently in children with OSA, related to the frequent associated arousals and an increased percentage of SWS.

One of the most important but frequently overlooked sequelae of OSA in children is the effect on mood, behavior, learning, and academic functioning. The neurobehavioral consequences of OSA in children include daytime sleepiness with drowsiness, difficulty in morning waking, and unplanned napping or dozing off during activities, although evidence of frank hypersomnolence tends to be less common in children compared to adults with OSA (except in very obese children). Mood changes include increased irritability, mood instability and emotional dysregulation, low frustration tolerance, and depression/anxiety. Behavioral issues include both “internalizing” (i.e., increased somatic complaints and social withdrawal) and “externalizing” behaviors, including aggression, impulsivity, hyperactivity, oppositional behavior, and conduct problems. There is a substantial overlap between the clinical impairments associated with OSA and the diagnostic criteria for ADHD, including inattention, poor concentration, and distractibility (see Chapter 33). There may be a selective impact of OSA specifically on “executive functions,” which include cognitive flexibility, task initiation, self-monitoring, planning, organization, and self-regulation of affect and arousal; executive function deficits are also a hallmark of ADHD.

Many of the studies that have looked at changes in behavior and neuropsychologic functioning in children following treatment (usually adenotonsillectomy) for OSA have largely documented significant improvement in outcomes, in both the short and long term, of OSA syndrome posttreatment, including daytime sleepiness, mood, behavior, academics, and quality of life. However, most studies failed to find a dose-dependent relationship between OSA in children and specific neurobehavioral/neurocognitive deficits, suggesting that other factors may influence neurocognitive outcomes, including individual genetic susceptibility, racial/ethnic background, environmental influences such as passive smoking exposure, and comorbid conditions, such as obesity, shortened sleep duration, and the presence of other sleep disorders. In adults, cognitive functions impacted by OSA include deficits in attention, long-term visual and verbal memory, visuospatial functioning, and executive function while language and psychomotor function do not appear to be impacted.

Diagnosis

The 2012 revised American Academy of Pediatrics clinical practice guidelines provide excellent information for the evaluation and management of uncomplicated childhood OSA (Table 19-5). There are no physical examination findings that are truly pathognomonic for OSA, and most healthy children with OSA appear normal; certain physical examination findings may suggest OSA. Growth parameters may be abnormal (obesity or, less commonly, failure to thrive), and there may be evidence of chronic nasal obstruction (hyponasal speech, mouth breathing, septal deviation, “adenoidal facies”), as well as signs of atopic disease (i.e., “allergic shiners”). Oropharyngeal examination may reveal enlarged tonsils, excess soft tissue in the posterior pharynx, and a narrowed posterior pharyngeal space. Any abnormalities of the facial structure, such as retrusion and/or micrognathia, midfacial hypoplasia, best appreciated by inspection of the lateral facial profile, increase the likelihood of OSA and should be noted. In very severe cases, there may be evidence of pulmonary hypertension, right-sided heart failure, and cor pulmonale; systemic hypertension may occur, especially in obese children.

Because no combination of clinical history and physical findings can accurately predict which children with snoring have OSA, the gold standard for diagnosing OSA remains an in-lab overnight polysomnogram.

Overnight PSG is a technician-supervised, monitored study that documents physiologic variables during sleep; sleep staging, arousal measurement, cardiovascular parameters, and body movements (electroencephalography, electrococoxylography, chin and leg electromyography, electrocardiogram, body position sensors, and video recording), and a combination of breathing monitors (oronasal thermal sensor and nasal air pressure transducer for airflow), chest/abdominal monitors (e.g., inductance plethysmography for respiratory effort, pulse oximeter for O₂ saturation, end-tidal or transtibial CO₂ for CO₂ retention, snore microphone). The polysomnographic parameter most commonly used in evaluating for sleep disordered breathing is the apnea-hypopnea index (AHI), which indicates the number of apneic and hypopneic events per hour of sleep. It should be noted that currently there are no universally accepted polysomnographic normal reference values and parameters for diagnosing OSA in children, and it is still unclear which parameters best predict morbidity. Normal preschool and school-age children generally have a total AHI of less than 1.5 (obstructive AHI <1), and this is the most widely used cutoff value for OSA in children 12 yr and below; in older adolescents, the adult cutoff of an AHI ≥5 is generally used. In cases in which the AHI
is between 1 and 5 obstructive events per hour, clinical judgment regarding risk factors for SDB, evidence of daytime sequelae, and the technical quality of the overnight sleep study should determine further management.

**Treatment**

There are presently no universally accepted guidelines regarding the indications for treatment of pediatric SDB (i.e., including primary snoring and OSA). Current recommendations largely emphasize weighing what is known about the potential cardiovascular, metabolic, and neurocognitive sequelae of SDB in children in combination with the individual healthcare professional’s clinical judgment. The decision of whether and how to treat OSA specifically in children is contingent on a number of parameters, including severity (nocturnal symptoms, daytime sequelae, sleep study results), duration of disease, and individual patient variables such as age, comorbid conditions, and underlying etiologic factors. Figure 19-1 presents a guide to decision making. In the case of moderate (AHI 5-10) to severe disease (AHI >10), the decision to treat is usually straightforward, and most pediatric sleep experts recommend that any child with an apnea hypopnea index >5 should be treated. However, a large randomized trial of early adenotonsillectomy vs watchful waiting with supportive care, 46% of the control group children normalized on PSG (compared to 79% of the early adenotonsillectomy group) during the 7 mo observation period.

In the majority of cases of pediatric OSA, adenotonsillectomy is the first-line treatment in any child with significant adenotonsillar hypertrophy, even in the presence of additional risk factors such as obesity. Adenotonsillectomy in uncomplicated cases generally (70-90% of children) results in complete resolution of symptoms; regrowth of adenoidal tissue after surgical removal occurs in some cases. Groups considered high-risk include young children (<3 yr old), as well as those with severe OSA documented by PSG, significant clinical sequelae of OSA (e.g., failure to thrive), or associated medical conditions, such as craniofacial syndromes, morbid obesity, and hypotonia. All patients should be reevaluated postoperatively to determine whether additional evaluation, a repeat polysomnogram and/or treatment are required. The American Academy of Sleep Medicine recommends that in high-risk groups (children with obesity, craniofacial anomalies, Down syndrome or moderate-severe OSA) or in children with continued symptoms of OSA, a follow-up sleep study at least 6 wk postadenotonsillectomy is indicated.

Additional treatment measures that may be appropriate include weight loss, positional therapy (attaching a firm object, such as a tennis ball, to the back of a sleep garment to prevent the child from sleeping in the supine position), and aggressive treatment of additional risk factors when present, such as asthma, seasonal allergies, and gastroesophageal reflux; there is evidence that intranasal corticosteroids and leukotriene inhibitors may be helpful in reducing upper airway inflammation in mild OSA. Other surgical procedures, such as
### Algorithm for the Diagnosis and Treatment of Pediatric OSA

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
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</table>
| Step 1. | Child is at risk for OSA (one or more):  
- Parents report symptoms of OSA  
- Physician identifies symptoms of OSA using structured questionnaire  
- Conditions predisposing to OSA are present (adenotonsilar hypertrophy, allergies, obesity, craniofacial abnormalities, neuromuscular disorders)  
- History of prematurity  
- Family history of OSA |
| Step 2a. | OSA-related morbidity is recognized (one or more):  
- Systolic or diastolic blood pressure >95th percentile for gender, age and height, or pulmonary hypertension  
- Daytime sleepiness, hyperactivity, inattention, academic difficulties  
- Inadequate somatic growth  
- Enuresis |
| Step 2b. | Conditions frequently coexisting with OSA are identified (one or more):  
- Recurrent otitis media, tympanostomy tubes  
- Recurrent wheezing  
- Oral-motor dysfunction  
- Metabolic syndrome |
| Step 3. | Factors predicting OSA persistence are present (at least one):  
- Male gender  
- Increasing Body Mass Index percentile, development of obesity |
| Step 4. | Objective evaluation for OSA severity:  
- Overnight polysomnography  
- If not available: nocturnal pulse oximetry |
| Step 5. | Child is a potential candidate for treatment if at risk for OSA (step 1) and at least one criterion:  
- AHI >5 episodes/h  
- AHI 1–5 and OSA morbidity present (step 2a)  
- AHI 1–5 and risk factor for OSA persistence (step 3)  
- AHI 1–5 and neuromuscular disorder or craniofacial abnormalities present (step 1)  
- ≥3 SpO2 drops <90% and ≥3 clusters of desaturation events or alternatively, desaturation (≥3%) index ≥3.5 episodes/h  
Or if polysomnography or oximetry not available:  
- Frequently or almost always loud snoring and male gender  
- Frequently or almost always loud snoring and sleepiness  
- Frequently or almost always loud snoring and learning problems |
| Step 6. | Stepwise treatment approach:  
1. Weight control for obesity  
2. Trial of nasal corticosteroids for adenoidal hypertrophy prior to adenoidectomy  
3. Adenotonsillectomy for adenotonsilar hypertrophy  
4. Orthodontic devices for mandibular malpositioning, narrow maxilla  
5. nCPAP for: i) residual OSA after adenotonsillectomy; ii) OSA related to obesity, neuromuscular disorders or craniofacial abnormalities and unresponsive to other measures  
6. Craniofacial surgery or tracheostomy if other treatment modalities fail |

**Notes**

1. Information collected in steps 1–4 is used to identify children requiring treatment for OSA (step 5) and to determine the appropriate therapeutic modalities (step 6). Please refer to the text for details.
2. Step 6 represents a hierarchical approach to OSA treatment.

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**Parasomnias**

Parasomnias are episodic nocturnal behaviors that often involve cognitive disorientation and autonomic and skeletal muscle disturbance. Parasomnias may be further characterized as occurring primarily during non-REM sleep (partial arousal parasomnias) or in association with REM sleep, including nightmares, hypnogogic hallucinations, and sleep paralysis; other common parasomnias include sleep-talking and hypnic jerks or “sleep starts” (Fig. 19-2). Sleep-related movement disorders, including restless legs syndrome/periodic limb movement disorder (RLS/PLMD) and rhythmical movement disorder (head banging, body rocking), are reviewed in “Sleep-Related Movement Disorders: Restless Legs Syndrome/Periodic Limb Movement Disorder and Rhythmic Movements” below.

**Etiology**

Partial arousal parasomnias, which include sleepwalking, sleep terrors, and confusional arousals are more common in preschool and school-age children because of the relatively higher percentage of SWS in younger children. They typically occur when SWS predominates (i.e., in the first third of the night); in contrast, nightmares, which are much more common than the partial arousal parasomnias but are often confused with them, are concentrated in the last third of the night, when REM sleep is most prominent. Any factor that is associated with an increase in the relative percentage of SWS (certain medications, previous sleep restriction) may increase the frequency of events.
Non-rapid eye movement sleep parasomnias.

REM behavior disorder.

NFLE, nocturnal frontal lobe epilepsy; RBD, REM sleep behavior disorder.

Other nocturnal spells that may be confused with parasomnias include sleepwalking and non-REM sleep, such as sleepwalking, occurring because of abnormal intrusions of wakefulness into non-REM sleep. Other nocturnal spells that may be confused with parasomnias include NFLE and sleep drunkenness, occurring because of abnormal intrusions of wakefulness into REM sleep and likewise non-REM parasomnias, such as sleepwalking, occurring because of abnormal intrusions of wakefulness into non-REM sleep. Other nocturnal spells that may be confused with parasomnias include NFLE and sleep drunkenness, occurring because of abnormal intrusions of wakefulness into REM sleep and likewise non-REM parasomnias, such as sleepwalking, occurring because of abnormal intrusions of wakefulness into non-REM sleep.

Because they typically occur at the transition out of "deep" or SWS, partial arousal parasomnias have clinical features of both the awake (ambulation, vocalizations) and the sleeping (high arousal threshold, unresponsiveness to the environment) states; there is usually amnesia for the events. The duration is typically a few minutes (sleep terrors) to 30-40 minutes (confusional arousals). Sleep terrors typically arise more gradually from sleep, may involve thrashing around but usually not displacement from bed, and are often accompanied by slow mentation, disorientation and confusion on forced arousal from SWS or upon waking in the morning. Sleepwalking may be associated with safety concerns (e.g., falling out of windows, wandering outside). Avoidance of, or increased agitation with, comforting by parents or attempts at awakening are also common features of all partial arousal parasomnias.

REM sleep behavior disorder, characterized by episodes of arousal during REM sleep, loss of REM atonia, and acting out of dreams including vocalizations during night-time sleep or naps. Some patients have CNS lesions (tumors), narcolepsy, seizures, neuropsychiatric medications, or neurodegenerative diseases.

Treatment

Management of partial arousal parasomnias involves some combination of parental education and reassurance, healthy sleep practices, and avoidance of exacerbating factors such as sleep restriction and caffeine. Particularly in the case of sleepwalking, it is important to institute safety precautions such as use of gates in doorways and at the top of staircases, locking of outside doors and windows, and installation of parent notification systems such as bedroom door alarms. Scheduled awakenings, a behavioral intervention that involves having the parent wake the child approximately 15-30 min before the time of night that the first parasomnia episode is most likely to be successful in situations in which partial arousal episodes occur on a nightly basis. Pharmacotherapy is rarely necessary, but may be indicated in cases of frequent or severe episodes, high risk of injury, violent behavior, or serious disruption to the family; the primary pharmacologic agents used are potent SWS suppressants, primarily benzodiazepines and tricyclic antidepressants.

Sleep-Related Movement Disorders: Restless Legs Syndrome/Periodic Limb Movement Disorder and Rhythmic Movements

RLS (Willis Ekbom syndrome) is a chronic neurologic disorder, characterized by an almost irresistible urge to move the legs, often accompanied by uncomfortable sensations in the lower extremities. Both the urge to move and the sensations are usually worse at rest and in the evening and are at least partially relieved by movement, including walking, stretching, and rubbing, but only as long as the motion continues. RLS is a clinical diagnosis that is based on the presence of these key symptoms. PLMD is characterized by periodic, repetitive, brief (0.5-10 sec), and highly stereotyped limb jerks typically occurring at 20-40 sec intervals. These movements occur primarily during sleep, most commonly occur in the legs, and frequently consist of rhythmic extension of the big toe and dorsiflexion at the ankle. The diagnosis of periodic limb movements (PLMs) requires overnight PSG to document the characteristic limb movements with anterior tibialis electromyography leads.

Etiology

“Early-onset” RLS (i.e., onset of symptoms before 35-40 yr of age), often termed “primary” RLS, appears to have a particularly strong genetic component, with a 6-7 fold increase in prevalence in first-degree relatives of RLS patients. The mode of inheritance is complex and several genetic loci have been identified (MEIS1, BTBD9, MAP2K5). Low serum iron levels in both adults and children may be an important etiologic factor for the presence and severity of both RLS symptoms and PLMs. As a marker of decreased iron stores, serum ferritin levels in both children and adults with RLS are frequently low (i.e., less than 50 µg/mL). The underlying mechanism that has been postulated is related to the role of iron as a cofactor in tyrosine hydroxylation, a rate-limiting step in dopamine synthesis; in turn, dopaminergic dysfunction has been implicated as playing a key role particularly in the genesis of the sensory component of RLS, as well as in PLMD. Certain medical conditions, including diabetes mellitus, end-stage renal disease, cancer, rheumatoid arthritis, hypothyroidism, and pregnancy, may also be associated with RLS/PLMD, as are specific medications.
(e.g., antihistamines such as diphenhydramine, antidepressants, and H₂ blockers such as cimetidine) and substances (notably, caffeine).

**Epidemiology**

Previous studies found prevalence rates of RLS in the pediatric population ranging from 1-6%; approximately 2% of 8-17 yr old meet the criteria for “definite” RLS. Prevalence rates of PLMs greater than 5 per hour in clinical populations of children referred for sleep studies range from 5-27%; in survey studies of PLM symptoms, rates are 8-12%. Several studies in referral populations have found that PLMs occur in as much as 25% of children diagnosed with ADHD.

**Clinical Manifestations**

In addition to the urge to move the legs and the sensory component, most RLS episodes begin or are exacerbated by rest or inactivity, such as lying in bed to fall asleep or riding in a car for prolonged periods. A unique feature of RLS is that the timing of symptoms also appears to have a circadian component, in that they often peak in the evening hours. Some children may complain of “growing pains,” although this is considered a nonspecific feature. Because RLS symptoms are usually worse in the evening, bedtime struggles and difficulty falling asleep are 2 of the most common presenting complaints. In contrast to patients with RLS, individuals with PLMs are usually unaware of these movements, but children may complain of morning muscle pain or fatigue; these movements may result in arousals during sleep and consequent significant sleep disruption. Parents of children with RLS/PLMD may report that their child is a restless sleeper, moves around or even falls out of bed during the night.

**Treatment**

The decision of whether and how to treat RLS depends on the level of severity (intensity, frequency, and periodicity) of sensory symptoms, the degree of interference with sleep, and the impact of daytime sequelae. With PLMs, for an index (PLMs per hour) less than 5, usually no treatment is recommended; for an index greater than 5, the decision to specifically treat PLMs should be based on the presence or absence of nocturnal symptoms (restless or nonrestorative sleep) and daytime clinical sequelae. The acronym AIMS represents a comprehensive approach to the treatment of RLS: A = avoidance of exacerbating factors such as caffeine and drugs which increase symptoms, I = iron supplementation when appropriate, M = muscle activity (increased physical activity, muscle relaxation, application of heat/cold compresses), and S = sleep (regular sleep schedule and sufficient sleep for age). Iron supplements should be instituted if serum ferritin levels are <50; it should be kept in mind that ferritin is an acute-phase reactant and thus may be falsely elevated (i.e., normal) in the setting of a concomitant illness. The recommended dose of ferrous sulfate is typically in the range of 3-6 mg/kg/day for a duration of 3 mo. Medications that increase dopamine levels in the CNS, such as ropinirole and pramipexole, have been found to be effective in relieving RLS/PLMD symptoms in adults; data in children are extremely limited.

**Sleep-related rhythmic movements**, including head banging, body rocking, and head rolling, are characterized by repetitive, stereotyped, and rhythmic movements or behaviors that involve large muscle groups. These behaviors typically occur with the transition at sleep at bedtime, but also at nap times and following nighttime arousals. Children typically engage in these behaviors as a means of soothing themselves to (or back to) sleep; they are much more common in the 1st yr of life and usually disappear by preschool age. In most instances, rhythmic movement behaviors are benign, because sleep is not significantly disrupted as a result of these movements and associated significant injury is rare. These behaviors typically occur in normally developing children, and in the vast majority of cases their presence does not indicate that there is some underlying neurologic or psychologic problem. Usually, the most important aspect in management of sleep-related rhythmic movements is reassurance to the family that this behavior is normal, common, benign, and self-limited.

**Narcolepsy**

*Hypersomnia* is a clinical term that is used to describe a group of disorders characterized by recurrent episodes of excessive daytime sleepiness (EDS), reduced baseline alertness, and/or prolonged nighttime sleep periods that interfere with normal daily functioning. It is important to recognize that there are many potential causes of EDS, which may be broadly grouped as “extrinsic” (e.g., secondary to insufficient and/or fragmented sleep) or “intrinsic” (e.g., resulting from an increased need for sleep). *Narcolepsy* is a chronic lifelong CNS disorder, typically presenting in adolescence and early adulthood, that is characterized by profound daytime sleepiness and resultant significant functional impairment. Other symptoms frequently associated with narcolepsy, including cataplexy (sudden and temporary loss of muscle tone), hypnagogic/hypnopompic (immediately before falling asleep/awakening) hallucinations, and sleep paralysis, may be conceptualized

---

**Table 19-6** Key Similarities and Differentiating Features Between Non-REM and REM Parasomnias as Well as Nocturnal Seizures

<table>
<thead>
<tr>
<th>Confusional Arousal</th>
<th>Sleep Terrors</th>
<th>Sleepwalking</th>
<th>Nightmares</th>
<th>RBD</th>
<th>Nocturnal Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>Early</td>
<td>Early-Mid</td>
<td>Late</td>
<td>Late</td>
<td>Any</td>
</tr>
<tr>
<td>Sleep stage</td>
<td>SWA</td>
<td>SWA</td>
<td>REM</td>
<td>REM</td>
<td>Any</td>
</tr>
<tr>
<td>EEG discharges</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Scream</td>
<td>–</td>
<td>–</td>
<td>++</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Autonomic activation</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Motor activity</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Awakens</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Duration (minutes)</td>
<td>0.5–10</td>
<td>1–10</td>
<td>2–30</td>
<td>3–20</td>
<td>1–10</td>
</tr>
<tr>
<td>Postevent confusion</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Age</td>
<td>Child</td>
<td>Child</td>
<td>Child–Young Adult</td>
<td>Older Adult</td>
<td>Adolescent, Young Adult</td>
</tr>
<tr>
<td>Genetics</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>±</td>
</tr>
<tr>
<td>Organic CNS lesion</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>++</td>
</tr>
</tbody>
</table>

EEG, Electroencephalogram; RBD, REM behavior disorder; REM, rapid eye movement; SWA, slow-wave arousal

as representing the “intrusion” of REM sleep features into the waking state (see further descriptions below).

**Etiology**
The genesis of narcolepsy with cataplexy (type 1) is thought to be related to a specific deficit in the hypothalamic orexin/hypocretin neurotransmitter system. The underlying pathogenesis of narcolepsy involves selective loss of cells that secrete hypocretin/orexin in the lateral hypothalamus; it has been postulated that autoimmune mechanisms, possibly triggered by viral infections, in combination with a genetic predisposition and environmental factors, may be involved. Human leukocyte antigen testing also shows a strong association with narcolepsy; however, the vast majority of individuals with this antigen do not have narcolepsy, and most (90%), but not all, patients with narcolepsy with cataplexy are HLA-DQB1*0602–positive. Patients with narcolepsy without cataplexy (type 2) are increasingly thought to have a significantly different pathophysiology; they are much less likely to be HLA-DQB1*0602–positive. Although the majority of cases of narcolepsy are considered idiopathic, “secondary” narcolepsy with cataplexy is associated with CNS insults, including hypothalamic tumors and cranial irradiation, and specific genetic syndromes (Prader-Willi [see Chapter 81.8] and Niemann-Pick type C [see Chapter 86.4]). Narcolepsy has been reported in Finnish children after immunization with the AS03 adjuvanted AH1N1 influenza vaccine.

**Epidemiology**
The prevalence of narcolepsy is reported to be between 3 and 16 per 10,000, with the prevalence of narcolepsy with cataplexy approximately 0.2-0.5/10,000. The risk of developing narcolepsy with cataplexy in a 1st-degree relative of a narcoleptic patient is estimated at 1-2%; this represents an increase of 10-40-fold compared to the general population.

**Clinical Manifestations and Diagnosis**
The typical onset of symptoms of narcolepsy is in adolescence and early adulthood, although symptoms may initially present in school-age and even younger children. The early manifestations of narcolepsy are often ignored, misinterpreted, or misdiagnosed as other medical, neurologic, and psychiatric conditions, and the appropriate diagnosis is frequently delayed for a number of years.

The most prominent clinical manifestation of narcolepsy is profound daytime sleepiness, characterized by both an increased baseline level of daytime drowsiness and by the repeated occurrence of sudden and unpredictable sleep episodes. These “sleep attacks” are often described as “irresistible” in that the child or adolescent is unable to stay awake despite considerable effort, and they occur even in the context of normally stimulating activities (e.g., during meals, in the middle of a conversation). Very brief (several seconds) sleep attacks may also occur in which the individual may “stare off,” appear unresponsive, or continue to engage in an ongoing activity (automatic behavior). EDS may also be manifested by increased nighttime sleep needs and extreme difficulty waking in the morning or after a nap.

**Cataplexy** is considered pathognomonic for narcolepsy. Cataplexy is rarely the first symptom of narcolepsy, but it often develops within the 1st yr of the onset of EDS. It is described as an abrupt, bilateral, partial (especially knees and head/jaw) or complete loss of muscle tone, without loss of consciousness, classically triggered by an intense positive emotion (e.g., laughter, surprise). The cataplectic attacks are typically brief (seconds to minutes) but in children may last for hours or days (“status cataplecticus”), and they are fully reversible, with complete recovery of normal tone when the episode ends. “Cataplectic facies” is a clinical feature unique to the pediatric population and is characterized by slack facial musculature, a protruding tongue, and slurred speech. **Hypnogogic/hypnopompic hallucinations** involve vivid visual, auditory, and sometimes tactile sensory experiences occurring during transitions between sleep and wakefulness, primarily at sleep offset (hypnopompic) and sleep onset (hypnogogic). **Sleep paralysis** is the inability to move or speak for a few seconds or minutes at sleep onset or offset, and often accompanies the hallucinations.

Other symptoms associated with narcolepsy include disrupted nocturnal sleep, impaired cognition, inattention, and behavioral and mood dysregulation.

Overnight PSG followed by a multiple sleep latency test are strongly recommended components of the evaluation of a patient with profound unexplained daytime sleepiness or suspected narcolepsy. The purpose of the overnight PSG is to evaluate for primary sleep disorders, such as OSA that may cause EDS. The multiple sleep latency test involves a series of 5 opportunities to nap (20 min long), during which narcoleptics demonstrate a pathologically shortened mean sleep onset latency (typically less than 5 minutes) as well as at least 2 periods of REM sleep occurring immediately after sleep onset.

**Treatment**
An individualized narcolepsy treatment plan usually involves education, good sleep hygiene, behavioral changes, and medication. Scheduled naps are often helpful. Medications such as psychostimulants and modafinil are often prescribed to control the EDS, whereas antidepressants (serotonin reuptake inhibitors, venlafaxine) may also be used to reduce cataplexy. Sodium oxybate is a drug that appears to both positively impact daytime sleepiness and REM-associated phenomena, such as cataplexy, hypnogogic hallucinations, and sleep paralysis. Most of these medications are not approved for use in children. The goal should be to allow the fullest possible return of normal functioning in school, at home, and in social situations.

**Delayed Sleep Phase Disorder**
**Delayed sleep phase disorder** (DSPD), a circadian rhythm disorder, involves a significant, persistent, and intractable phase shift in sleep–wake schedule (later sleep onset and wake time) that conflicts with the individual’s normal school, work, and/or lifestyle demands. DSPD may occur at any age, but is most common in adolescents and young adults.

**Etiology**
Individuals with DSPD often start out as night owls; that is, they have an underlying predisposition or circadian preference for staying up late at night and sleeping late in the morning, especially on weekends, holidays, and summer vacations. The underlying pathophysiology of DSPD is still unknown, although some authors have theorized that it involves an intrinsic abnormality in the circadian oscillators that govern the timing of the sleep period.

**Epidemiology**
Studies indicate that the prevalence of DSPD may be as high as 7-16% in adolescents and young adults.

**Clinical Manifestations**
The most common clinical presentation is sleep initiation insomnia when the individual attempts to fall asleep at a “socially acceptable” desired bedtime, accompanied by extreme difficulty getting up in the morning even for desired activities, and daytime sleepiness. Sleep maintenance is generally not problematic, and no sleep onset insomnia is experienced if bedtime coincides with the preferred sleep onset time (e.g., on weekends, school vacations). School tardiness and frequent absenteeism with a decline in academic performance are often present.

**Treatment**
The treatment of DSPD usually has 3 components, all directed toward the goals of shifting the sleep–wake schedule to an earlier more desirable time, and maintaining the new schedule. The initial step involves shifting the sleep–wake schedule to the desired earlier times, usually with gradual (i.e., in 15-30 min increments every few days) advancement of bedtime in the evening and rise time in the morning; more significant phase delays (i.e., difference between current sleep onset and desired bedtime) may require “chronotherapy,” which involves delaying bedtime and wake time by 2-3 hr every 24 hr “forward around the clock” until the target bedtime is reached. Because melatonin secretion is highly sensitive to light, exposure to light in the morning (either natural light or a “light box,” which typically produces predominantly
blue light) and avoidance of evening light exposure are often beneficial. Exogenous oral melatonin supplementation may also be used; larger mildly sedating doses (i.e., 5 mg) are typically given at bedtime, but some studies have suggested that physiologic doses of oral melatonin (0.3-0.5 mg) administered in the afternoon or early evening (i.e., 5-7 hr before the habitual sleep onset time) seem to be most effective in advancing the sleep phase.

**HEALTH SUPERVISION**

It is especially important for pediatricians to both screen for and recognize sleep disorders in children and adolescents during health encounters. The well-child visit is an opportunity to educate parents about normal sleep in children and to teach strategies to prevent sleep problems from developing (primary prevention) or from becoming chronic, if problems already exist (secondary prevention). Developmentally appropriate screening for sleep disturbances should take place in the context of every well child visit and should include a range of potential sleep problems; one Table 19-7 outlines a simple sleep screening algorithm, the “BEARS.” Because parents may not always be aware of sleep problems, especially in older children and adolescents, it is also important to question the child directly about sleep concerns. The recognition and evaluation of sleep problems in children requires both an understanding of the association between sleep disturbances and daytime consequences, such as irritability, inattention, and poor impulse control, and familiarity with the developmentally appropriate differential diagnoses of common presenting sleep complaints (difficulty initiating and maintaining sleep, episodic nocturnal events). In particular, an assessment of sleep patterns and possible sleep problems should be part of the initial evaluation of every child presenting with behavioral and/or academic problems, especially ADHD.

Effective preventive measures include educating parents of newborns about normal sleep amounts and patterns. The ability to regulate sleep, or control internal states of arousal to fall asleep at bedtime and to fall back asleep during the night, begins to develop in the 1st 8-12 wk of life. Thus, it is important to recommend that parents put their 2-4 mo old infants to bed “drowsy but awake” if they wish to avoid dependence on parental presence at sleep onset and foster the infants’ ability to self-soothe. Other important sleep issues include discussing the importance of regular bedtimes, bedtime routines, and transitional objects for toddlers, and providing parents and children with basic information about healthy sleep practices, recommended sleep amounts at different ages, and education regarding signs that a child is not getting sufficient sleep (i.e., wakes with difficulty in the morning, sleeps longer when allowed on weekends and vacation days).

The cultural and family context within which sleep problems in children occur should be considered; for example, cosleeping of infants and parents is a common and accepted practice in many racial/ethnic groups and the goal of independent self-soothing in young infants may not be shared by these families. Anticipatory guidance needs to balance cultural awareness with the critical importance of “safe sleep” conditions in sudden infant death syndrome prevention (i.e., sleeping in the supine position, avoidance of bed-sharing but encouragement of room-sharing in the 1st yr of life) (see Chapter 375). On the other hand, the institution of cosleeping by parents as an attempt to address a child’s underlying sleep problem (so-called reactive cosleeping), rather than as a conscious family decision, is likely to yield only a temporary reprieve from the problem and may set the stage for more significant sleep issues.

**EVALUATION OF PEDIATRIC SLEEP PROBLEMS**

The clinical evaluation of a child presenting with a sleep problem involves obtaining a careful medical history to assess for potential medical causes of sleep disturbances, such as allergies, concomitant medications, and acute or chronic pain conditions. A developmental history is important because of the aforementioned increased risk of sleep problems in children with neurodevelopmental disorders.

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**Table 19-7 BEARS Sleep Screening Algorithm**

The BEARS instrument is divided into 5 major sleep domains, providing a comprehensive screen for the major sleep disorders affecting children 2-18 yr old. Each sleep domain has a set of age-appropriate “trigger questions” for use in the clinical interview.

- **B** = Bedtime problems
- **E** = Excessive daytime sleepiness
- **A** = Awakenings during the night
- **R** = Regularity and duration of sleep
- **S** = Snoring

**Examples of Developmentally Appropriate Trigger Questions**

<table>
<thead>
<tr>
<th>TODDLER/PRESCHOOL CHILD (2-5 YR)</th>
<th>SCHOOL-AGED CHILD (6-12 YR)</th>
<th>ADOLESCENT (13-18 YR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Bedtime problems</strong>&lt;br&gt;Does your child have any problems going to bed? Falling asleep?</td>
<td><strong>Does your child have any problems going to bed? (P)</strong>&lt;br&gt;Do you have any problems waking up in the morning?</td>
<td><strong>Do you have any problems falling asleep at bedtime? (C)</strong>&lt;br&gt;Do you feel sleepy a lot during the day?</td>
</tr>
<tr>
<td><strong>2. Excessive daytime sleepiness</strong>&lt;br&gt;Does your child seem overtired or sleepy a lot during the day? Does your child still take naps?</td>
<td><strong>Does your child have difficulty waking in the morning, seem sleepy during the day, or take naps? (P)</strong>&lt;br&gt;Do you feel tired a lot? (C)</td>
<td><strong>Do you feel sleepy a lot during the day? In school? While driving? (C)</strong>&lt;br&gt;Do you wake up a lot at night? Do you have trouble getting back to sleep? (C)</td>
</tr>
<tr>
<td><strong>3. Awakenings during the night</strong>&lt;br&gt;Does your child wake up a lot at night?</td>
<td><strong>Does your child seem to wake up a lot at night? Any sleepwalking or nightmares? (P)</strong>&lt;br&gt;Do you wake up a lot at night? Do you have trouble getting back to sleep? (C)</td>
<td><strong>Do you wake up a lot at night?</strong>&lt;br&gt;Do you have trouble getting back to sleep? (C)</td>
</tr>
<tr>
<td><strong>4. Regularity and duration of sleep</strong>&lt;br&gt;Does your child have a regular bedtime and wake time? What are they?</td>
<td><strong>What time does your child go to bed and get up on school days? Weekends? Do you think your child is getting enough sleep? (P)</strong></td>
<td><strong>What time do you usually go to bed on school nights? Weekends? How much sleep do you usually get? (C)</strong></td>
</tr>
<tr>
<td><strong>5. Snoring</strong>&lt;br&gt;Does your child snore a lot or have difficulty breathing at night?</td>
<td><strong>Does your child have loud or nightly snoring or any breathing difficulties at night? (P)</strong></td>
<td><strong>Does your teenager snore loudly or nightly? (P)</strong></td>
</tr>
</tbody>
</table>

C, child; P, parent.
Assessment of the child's current level of functioning (school, home) is a key part of evaluating possible mood, behavioral, and neurocognitive sequelae of sleep problems. Current sleep patterns, including the usual sleep duration and sleep-wake schedule, are often best assessed with a sleep diary, in which a parent (or adolescent) records daily sleep behaviors for an extended period (1-2 wk). A review of sleep habits, such as bedtime routines, daily caffeine intake, and the sleeping environment (e.g., temperature, noise level) may reveal environmental factors that contribute to the sleep problems. Nocturnal symptoms that may be indicative of a medically based sleep disorder, such as OSA (loud snoring, choking or gasping, sweating) or PLMs (restless sleep, repetitive kicking movements), should be elicited. An overnight sleep study is not routinely warranted in the evaluation of a child with sleep problems unless there are symptoms suggestive of OSA or periodic leg movements, unusual features of episodic nocturnal events, or daytime sleepiness that is unexplained.

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Bottom of form.
It is estimated that 13-20% of children living in the United States experience a mental illness in a given year, at a cost of nearly $300 billion. In children, mental illness is more prevalent than leukemia, diabetes, and AIDS combined; more money is spent on mental disorders than on any other childhood illness, including asthma, trauma, upper respiratory infections, and infectious diseases. Although nearly 1 in 5 youths suffers from a psychiatric disorder, 75-80% do not receive needed mental health services. Those who do, primarily receive services in nonspecialty sectors (primary care, schools, child welfare, juvenile justice) where mental health expertise may be limited. Untreated or inadequately treated psychiatric disorders are associated with significant adverse sequelae, including increased morbidity and mortality, failure to achieve mastery in life's developmental tasks (education, occupation, marriage, child-rearing), cross-generational transmission of disadvantage, and substantial costs to society. Psychiatric disorders negatively affect the course of physical illness, adherence to treatment regimens, and use of medical resources. The strong continuity into adulthood of child psychiatric disorders further underscores the importance of early identification and treatment.

**AIMS OF ASSESSMENT**

A psychosocial assessment in the pediatric setting should determine whether there are signs and symptoms of cognitive, developmental, emotional, behavioral, or social difficulties and characterize these signs and symptoms sufficiently to determine their appropriate management. The focus of the assessment varies with the nature of the presenting problem and the clinical setting. Under emergency circumstances, the focus may be limited to an assessment of dangerousness to self or others for the purpose of determining the safest level of care. In routine circumstances (well-child visits), the focus may be broader, involving a screen for symptoms and functional impairment in all major psychosocial domains. The challenge for the pediatric practitioner will be to determine as accurately as possible whether the presenting signs and symptoms are likely to meet criteria for a psychiatric disorder and whether the severity and complexity of the disorder suggests referral to a mental health specialist or management in the pediatric setting.

**PRESENTING PROBLEMS**

*Infants* are presented for clinical attention because of problems with eating and/or sleep regulation, concerns about failure to gain weight and length, poor social responsiveness, limited vocalization, apathy or disinterest, and response to strangers that is excessively fearful or overly familiar. Psychiatric disorders most commonly diagnosed during this period are rumination and reactive attachment disorders.

*Toddlers* are assessed for concerns about sleep problems, language delay, motor hyperactivity, extreme misbehavior, extreme shyness, inflexible adherence to routine, difficulty separating from parents, struggles over toilet training, dietary issues, and testing limits. Developmental delays and more subtle physiologic, sensory, and motor processing problems can be presented as concerns. Problems with goodness of fit between the child's temperament and the parents' expectations can create relationship difficulties that also require assessment. Psychiatric disorders most commonly diagnosed during this period are autism spectrum and reactive attachment disorders.

Presenting problems in *preschoolers* include elimination difficulties, sibling jealousy, lack of friends, self-destructive impulsiveness, multiple fears, nightmares, refusal to follow directions, somatization, speech that is difficult to understand, and temper tantrums. Psychiatric disorders most commonly diagnosed in this period are autism spectrum, communication, disruptive, attention-deficit/hyperactivity, anxiety (separation, selective mutism), reactive attachment, gender dysphoria, and sleep disorders.

*Older children* are brought to clinical attention because of concerns about angry or sad mood, bedwetting, overactivity, impulsiveness, distractibility, learning problems, arguing, defiance, nightmares, school refusal, bullying or being bullied, worries and fears, somatization, communication problems, tics, and withdrawal or isolation. Psychiatric disorders most commonly diagnosed during this period are attention-deficit/hyperactivity, disruptive, anxiety (generalized, phobias), elimination, somatic symptom, specific learning, and tic disorders.

*Adolescents* are assessed for concerns about the family situation, experimentation with sexuality and drugs, delinquency and gang involvement, friendship patterns, issues of independence, identity formation, self-esteem, and morality. Psychiatric disorders most commonly diagnosed during this period are anxiety (panic, social anxiety), depressive, bipolar, psychotic, obsessive-compulsive, impulse control, conduct, substance-related, and eating disorders.

**GENERAL PRINCIPLES OF THE PSYCHOSOCIAL INTERVIEW**

Psychosocial interviewing in the context of a routine pediatric visit requires adequate time and privacy. The purpose of this line of inquiry should be explained to the child and parents (“to make sure things are going OK at home, at school, and with friends”), along with the limits of confidentiality. Thereafter, the first goal of the interview is to build rapport with both the child and the parents.

With the parents, this rapport is grounded in respect for the parents' knowledge of their child, their role as the central influence in their child's life, and their desire to make a better life for their child. Parents often feel anxious or guilty because they believe that problems in a child imply that their parenting skills are inadequate. Parents' experiences of their own childhood influence the meaning a parent places on a child's feelings and behavior. A good working alliance allows mutual discovery of the past as it is active in the present and permits potential distortions to be modified more readily. Developmentally appropriate overtures can facilitate rapport with the child. Examples include playing peek-a-boo with an infant, racing toy cars with a preschooler, commenting on sports with a child who is wearing a baseball cap, and discussing music with a teenager who is wearing a rock music t-shirt.

After an overture with the child, it is helpful to begin with family-centered interviewing, in which the parent is invited to present any psychosocial concerns (development, thinking, feelings, behavior, peer relationships) about the child. With adolescent patients, it is important to conduct a separate interview to give the adolescent an opportunity to confirm or refute the parent's presentation and to present the problem from his or her perspective. Following the family's undirected presentation of the primary problem, it is important to shift to direct questioning to clarify the duration, frequency, and severity of symptoms, associated distress or functional impairment, and the developmental and environmental context in which the symptoms occur.

Because of the high degree of comorbidity of psychosocial problems in children, after eliciting the presenting problem, the pediatric practitioner should then briefly screen for problems in all of the major
developmentally appropriate categories of cognitive, developmental, emotional, behavioral, and social disturbance, including problems with mood, anxiety, attention, behavior, thinking and perception, substance use, social relatedness, eating, elimination, development, language, and learning. This can be preceded by a transition statement such as, “Now I’d like to ask about some other issues that I ask all parents and kids about.”

A useful guide for this area of inquiry is provided by the “11 Action Signs” (Table 20–1), which was designed to give frontline clinicians the tools needed to recognize early symptoms of mental disorders. Functional impairment can be assessed by inquiring about symptoms and function in the major life domains, including home and family, school, peers, and community. These domains are included in the HEADSS (home, education, activities, drugs, sexuality, suicide/depression) interview guide, often used in the screening of adolescents (Table 20–2).

The nature and severity of the presenting problem(s) can be further characterized through the use of a standardized self-, parent-, or teacher-informant rating scale (Table 20–3 lists some of the scales in the public domain). A rating scale is a type of measure that provides a relatively rapid assessment of a specific construct with an easily derived numerical score that is readily interpreted. The use of rating scales can ensure systematic coverage of relevant symptoms, quantify symptom severity, and document a baseline against which treatment effects can be measured.

Clinical experience and methodologic studies suggest that parents and teachers are more likely than the child to report externalizing problems (disruptive, impulsive, overactive, or antisocial behaviors). Children may be more likely to report anxious or depressive feelings, including suicidal thoughts and acts, of which the parents may be unaware. Functional impairment also can be assessed with self and other rating scales. Although concerns have been raised about children’s competence as self-reporters (because of limitations in linguistic skills; self-reflection; emotional awareness; ability to monitor behavior, thoughts, and feelings; and tendency toward social desirability), children and adolescents can be reliable and valid self-reporters.

Clinicians are encouraged to become familiar with the psychometric characteristics and appropriate use of at least 1 broad-based measure of psychosocial problems, such as the Strengths and Difficulties Questionnaire (SDQ) (http://www.sqinfo.org/py/sqinfo/b0.py), the Pediatric Symptom Checklist (PSC) (http://www.brighterfutures.org/mentalhealth/pdf/professionals/ped_symptom_chklst.pdf), or the Swanson, Nolan, and Pelham–IV (SNAP-IV) (http://psychiatryassociatespc.com/doc/SNAP-IV_Parent&Teacher.pdf). These measures are available in multiple languages. If the interview or broad-based rating scale suggests difficulties in one or more specific symptom areas, the clinician can follow with a psychometrically sound, appropriate narrow-band instrument such as the Vanderbilt ADHD Diagnostic Rating Scale for attention, behavior, and learning problems, the Center for Epidemiological Studies Depression Scale for Children (CES-DC) or Mood and Feelings

<table>
<thead>
<tr>
<th>Table 20-1</th>
<th>Mental Health Action Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Feeling very sad or withdrawn for more than 2 weeks</td>
<td></td>
</tr>
<tr>
<td>• Seriously trying to harm or kill yourself, or making plans to do so</td>
<td></td>
</tr>
<tr>
<td>• Sudden overwhelming fear for no reason, sometimes with a racing heart or fast breathing</td>
<td></td>
</tr>
<tr>
<td>• Involvement in many fights, using a weapon, or wanting to badly hurt others</td>
<td></td>
</tr>
<tr>
<td>• Severe out-of-control behavior that can hurt yourself or others</td>
<td></td>
</tr>
<tr>
<td>• Not eating, throwing up, or using laxatives to make yourself lose weight</td>
<td></td>
</tr>
<tr>
<td>• Intense worries or fears that get in the way of your daily activities</td>
<td></td>
</tr>
<tr>
<td>• Extreme difficulty in concentrating or staying still that puts you in physical danger or causes school failure</td>
<td></td>
</tr>
<tr>
<td>• Repeated use of drugs or alcohol</td>
<td></td>
</tr>
<tr>
<td>• Severe mood swings that cause problems in relationships</td>
<td></td>
</tr>
<tr>
<td>• Drastic changes in your behavior or personality</td>
<td></td>
</tr>
</tbody>
</table>

From The Action Signs Project, Center for the Advancement of Children’s Mental Health at Columbia University.

<table>
<thead>
<tr>
<th>Table 20-2</th>
<th>HEADSS Screening Interview for Taking a Rapid Psychosocial History</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PARENT INTERVIEW</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Home</strong></td>
<td></td>
</tr>
<tr>
<td>• How well does the family get along with each other?</td>
<td></td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
</tr>
<tr>
<td>• How well does your child do in school?</td>
<td></td>
</tr>
<tr>
<td><strong>Activities</strong></td>
<td></td>
</tr>
<tr>
<td>• What does your child like to do?</td>
<td></td>
</tr>
<tr>
<td>• Does your child do anything that has you really concerned?</td>
<td></td>
</tr>
<tr>
<td><strong>Drugs</strong></td>
<td></td>
</tr>
<tr>
<td>• Has your child used drugs or alcohol?</td>
<td></td>
</tr>
<tr>
<td><strong>Sexuality</strong></td>
<td></td>
</tr>
<tr>
<td>• Are there any issues regarding sexuality or sexual activity that are of concern to you?</td>
<td></td>
</tr>
<tr>
<td><strong>Suicide/depression</strong></td>
<td></td>
</tr>
<tr>
<td>• Has your child ever been treated for an emotional problem?</td>
<td></td>
</tr>
<tr>
<td>• Has your child ever intentionally tried to hurt him-/herself or made threats to others?</td>
<td></td>
</tr>
</tbody>
</table>

| **ADOLESCENT INTERVIEW** |
| **Home** |
| • How do you get along with your parents? |
| **Education** |
| • How do you like school and your teachers? |
| • How well do you do in school? |
| **Activities** |
| • Do you have a best friend or group of good friends? |
| • What do you like to do? |
| **Drugs** |
| • Have you used drugs or alcohol? |
| **Sexuality** |
| • Are there any issues regarding sexuality or sexual activity that are of concern to you? |
| **Suicide/depression** |
| • Everyone feels sad or angry some of the time. How about you? |
| • Did you ever feel so upset that you wished you were not alive or so angry you wanted to hurt someone else badly? |


Questionnaire (MFQ) for depression, or the Screen for Child Anxiety Related Emotional Disorders (SCARED) for anxiety.

Children and adolescents scoring above standardized cutpoints in most cases should be referred to a qualified mental health professional for assessment and treatment, because scores in this range are highly correlated with clinically significant psychiatric disorders. Youths scoring just below or slightly above cutpoints (e.g., subsyndromal or mild mood, anxiety, or disruptive behavior disorders) may be appropriate for management in the pediatric setting, as may youths scoring well above cutpoints for certain neurodevelopmental disorders (attention-deficit/hyperactivity, autism spectrum, tic).

The safety of the child in the context of the home and community is of paramount importance. The interview should sensitively assess whether the child has been exposed to any frightening events, including abuse, neglect, bullying, marital discord, or domestic or community violence; whether the child shows any indication of dangerousness to self or others or a severely altered mental status (psychosis, intoxication, rage, hopelessness); or whether the child (if age-appropriate) has been involved in any risky behavior, including running away, staying out without permission, truancy, gang involvement, experimentation with substances, and unprotected sexuality. The interview also should assess the capacity of the parents to adequately provide for the child’s
The focus of the evaluation is developmental; it seeks to describe the child's functioning in various realms and to assess the child's adaptation in these areas relative to that expected for the child's age and phase of development. The developmental perspective extends beyond current difficulties to vulnerabilities that can affect future development and as such are important targets for preventive intervention. Vulnerabilities may include subthreshold or subsyndromal difficulties that, especially when manifold, often are accompanied by significant distress or impairment and as such are important as potential harbingers of future problems.

Throughout the assessment, the clinician focuses on identifying a realistic balance of vulnerabilities and strengths in the child, in the parents, and in the parent–child interactions. From this strength-based approach, over time a hopeful family narrative is co-constructed to frame the child's current developmental progress and predict the child's ongoing progress within the scope of current risk and protective factors.

Although the scope of the evaluation will vary with the clinical circumstance, the full psychiatric diagnostic evaluation has 12 major components: the presenting problem(s) and the context in which they occur; a review of psychiatric symptoms; a risk assessment; a history of psychiatric treatment; a medical history, a developmental history; an educational history; a family history; a mental status examination; a biopsychosocial clinical formulation; a Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnosis; and a treatment plan. For infants and young children, the presenting problem and historical information is derived from parents and other informants. As children mature, they become increasingly important contributors to the information base, and they become the primary source of information in later adolescence. Information relevant to formulation and differential diagnosis is derived in multiple ways, including directive and nondirective questioning, interactive play, and observation of the child alone and together with the caregiver(s).

The explication of the presenting problem(s) includes information about onset, duration, frequency, and severity of symptoms, associated physical, emotional, and social needs or whether parental capacity has been diminished by psychiatric disorder, family dysfunction, or the sequelae of disadvantaged socioeconomic status. Any indications of threats to the child's safety should be immediately followed by thorough assessment and protective action.

**INDICATIONS FOR REFERRAL**

There is variability in the level of confidence pediatric practitioners perceive in diagnosing psychosocial problems in children and adolescents. Pediatric practitioners who have familiarity with psychiatric diagnostic criteria may feel confident diagnosing certain disorders, particularly the neurodevelopmental and other biologically based disorders (attention-deficit/hyperactivity, autism spectrum, and tic disorders, enuresis, encopresis, insomnia, anorexia). The disorders about which pediatric practitioners might have less diagnostic confidence include the disruptive/impulse control/conduct, depressive, bipolar, anxiety, psychotic, obsessive-compulsive, trauma-related, somatic symptom, and substance-related disorders. Pediatric practitioners should refer to a qualified mental health practitioner whenever they experience diagnostic uncertainty with a child who has distressing or functionally impairing psychosocial symptoms. Children who upon initial assessment are found to have indicators of dangerousness always should be immediately referred to a qualified mental health professional.

### PSYCHIATRIC DIAGNOSTIC EVALUATION

The objectives of the psychiatric diagnostic evaluation of the child and adolescent are to determine whether psychopathology or developmental risk is present and if so, to establish an explanatory formulation and a differential diagnosis, and to determine whether treatment is indicated and if so, to develop a treatment plan and facilitate the parents' and child's involvement in the plan. The aims of the diagnostic evaluation are to clarify the reasons for the referral; to obtain an accurate accounting of the child's developmental functioning and the nature and extent of the child's psychosocial difficulties, functional impairment, and subjective distress; and to identify potential individual, family, or environmental factors that might account for, influence, or ameliorate these difficulties. The issues relevant to diagnosis and treatment planning can span genetic, constitutional, and temperamental factors; individual psychodynamics; cognitive, language, and social skills; family patterns of interaction and child-rearing practices; and community, school, and socioeconomic influences.

The objectives of the psychiatric diagnostic evaluation of the child and family, or environmental factors that might account for, influence, or ameliorate these difficulties. The issues relevant to diagnosis and treatment planning can span genetic, constitutional, and temperamental factors; individual psychodynamics; cognitive, language, and social skills; family patterns of interaction and child-rearing practices; and community, school, and socioeconomic influences.
distress and/or functional impairment, and predisposing, precipitating, perpetuating, and ameliorating contextual factors. The *symptom review* assesses potential comorbidity in the major domains of child and adolescent psychopathology, including problems with intellectual, communication, motor, learning, and developmental capabilities; attention deficits; angry, sad, or elated mood; anxiety; obsessions or compulsions; trauma or stress reactions; somatic symptoms; eating, elimination, sleep, or gender disturbances; disruptive, impulse-control, or conduct problems; psychosis; or substance abuse or addiction. The *risk assessment* includes a careful assessment of risk status, including suicidality, homicidality, assaultiveness, self-injuriousness, and involvement in risky behavior or situations. The *history of psychiatric treatment* includes gathering information about prior emergency mental health assessments, psychiatric hospitalizations, day treatment, psychotherapy, pharmacotherapy, and nontraditional treatments.

The *medical history* includes information about the source of primary care, the frequency of health supervision, past and current medical illnesses and treatments, and the youth and family's history of adherence to medical treatment. A systematic review of organ or functional systems facilitates the identification of abnormalities that require investigation or monitoring by the pediatric practitioner, as well as the identification of cautionary factors related to the prescription of psychotropic medication. The *developmental history* includes information about the circumstances of conception, pregnancy, or adoption; pre-, peri-, or postnatal insults; attachment and temperament; cognitive, motor, linguistic, emotional, social, and moral development; health habits, sexuality, and substance use (as age-appropriate), coping and defensive structure, future orientation, and perceived strengths. The *educational history* includes schools attended; typical grades, attendance, and behavior; special education services; disciplinary actions; social relationships; extracurricular activities; and barriers to learning. The *family history* assesses family composition; sociodemographic and neighborhood characteristics; domiciliary arrangements; parenting capacities; family function; medical and psychiatric histories of family members; and cultural/religious affiliations. The *mental status examination* assesses appearance, relatedness, cognition, communication, mood, affective expression, behavior, memory, orientation, and perception.

The evaluation culminates in a *biopsychosocial formulation and diagnosis*. The *biopsychosocial formulation* is derived from an assessment of vulnerabilities and strengths in the biologic, psychologic, and social domains and serves to identify targets for intervention and treatment. In the biologic domain, major vulnerabilities include a family history of psychiatric disorder and personality or behavior problems, and a personal history of pre-, peri-, or postnatal insults; cognitive or linguistic impairments; physical illness; and a difficult temperament. In the psychological domain, major vulnerabilities include failure to achieve developmental tasks and maladaptive coping and defensive styles. In the social domain, major vulnerabilities include parental incapacity; unskilled parenting; family dysfunction; social isolation; unfavorable school setting; unsupportive community structures; and sociodemographic disadvantage. Major strengths include cognitive and linguistic capability; physical health and attractiveness; stable, moderate temperamental characteristics; and stable and supportive parenting, family, peer, and community structures. The biopsychosocial formulation can be organized to reflect predisposing, precipitating, perpetuating, and protective (ameliorating) factors (the "4 Ps") influencing the development of the observed psychopathology.

The *diagnosis* must be made in accordance with the nomenclature in the DSM-5. This nomenclature categorizes cross-sectional phenomenology into discrete clinical syndromes and seeks to improve diagnostic accuracy at the expense of theories of causation and dimensional presentations. By DSM-5 convention, if diagnostic criteria are met, the diagnosis is given (except where hierarchical rules apply); consequently psychiatric comorbidity is a common occurrence.

The psychiatric diagnostic evaluation culminates in a *treatment plan* that brings the broad array of targeted psychosocial interventions to the service of the child. Diagnoses drive the choice of evidence-based psychotherapeutic and psychopharmacologic treatments. The formul-
Bibliography


Three-quarters of children with mental health problems are seen in primary care. About half of the treatment for psychiatric disorders is provided in primary care settings and most psychotropic prescriptions for youth are written by primary care practitioners. Barriers that prevent children and their families from obtaining needed mental health services include stigma, shortages of mental health...
professionals, inadequate coverage of mental health services in public and private health insurance programs, inadequately trained clinicians, inadequate time for primary care providers to identify mental health issues, and fragmented service delivery systems.

The provision of supportive counseling, anticipatory guidance, and parent psychoeducation about mental health problems combined with medication management of neurodevelopmental (attention-deficit/hyperactivity [ADHD], autism spectrum, tic), sleep, and elimination disorders are commonly undertaken by the pediatric practitioner. Youth with other psychiatric disorders (psychotic, bipolar, depression, anxiety, obsessive-compulsive, trauma-related, somatic symptom, dissociative, gender dysphoric, disruptive/impulse-control/conduct, and substance-related) require initial evaluation, treatment planning, and stabilization by child-trained mental health clinicians. However, the pediatric practitioner often resumes the care of these youth once stabilized.

Barriers to providing mental health services in the primary care setting include lack of mental health training for staff, insufficient time, lack of knowledge about community mental healthcare resources, and inadequate reimbursement. In the face of these challenges, safe and effective mental healthcare of children and adolescents requires effective collaboration between pediatric and mental health practitioners. Several models of effective collaboration in the primary care setting have been advanced; most converge in recommending the following components: (1) screening for and early detection of mental health problems; (2) triage/referral to appropriate mental health treatment; (3) timely access to mental health consultation and direct mental health assessment (in-person or via telepsychiatry); (4) care coordination (by a designated care coordinator in the primary care setting); (5) access to specialty mental health treatment services; and (6) education of primary care practitioners around the accurate assessment and safe and effective treatment of child and adolescent psychiatric disorders.

Bibliography is available at Expert Consult.

### 21.1 Psychopharmacology

David R. DeMaso and Heather J. Walter

Data are available regarding the safety and efficacy for the use of single psychotropic medications for the treatment of a number of childhood psychiatric disorders, including depressive, obsessive-compulsive, ADHD, anxiety, bipolar, psychotic, and tic disorders. Evidence also supports the use of psychotropic medications for agitation, aggression and serious problems with impulse control in disruptive/impulse-control/conduct and autism spectrum disorders.

The evidence for using multiple psychotropic medications at the same time is much smaller. Combinations of medications are used to address complex comorbid conditions, manage side effects, increase treatment response, and/or address symptoms hypothesized to be associated with multiple underlying neurotransmitter abnormalities (dopamine agonists for hyperactivity and serotonin agonists for anxiety).

To ensure safe and appropriate use of psychotropic medications, prescribers should follow best practice principles that underlie medication prescribing (Table 21-1). The use of medication involves a series of interconnected steps, including performing an assessment, deciding on treatment and a monitoring plan, obtaining treatment assent and/or consent, and implementing treatment. Cognitive, emotional, and/or behavior symptoms are targets for medication intervention when there is no response to available evidence-based psychosocial interventions, there is a significant risk of harm, and/or there is significant distress or functional impairment. Commonly encountered target symptom domains include agitation, aggression, anxiety, depression, hyperactivity, inattention, impulsivity, mania, and psychosis (Table 21-2).

### STIMULANTS AND OTHER ADHD MEDICATIONS

Stimulants are sympathomimetic drugs that act both in the central nervous system and peripherally by enhancing dopaminergic and noradrenergic transmission (Table 21-3). There is strong evidence for the effectiveness of these medications for the treatment of ADHD (number needed to treat [NNT] approximates 4) as well as aggression (NNT approximates 4), and moderate evidence for the treatment of hyperactivity in autism spectrum disorder. In some cases, stimulants are used as an adjunct in the treatment of depression and for fatigue

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**Table 21-1** Best Principles for Use of Psychotropic Medications

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Before initiating pharmacotherapy, a psychiatric evaluation is completed.</td>
</tr>
<tr>
<td>2.</td>
<td>Before initiating pharmacotherapy, a medical history is obtained and a medical evaluation is considered when appropriate.</td>
</tr>
<tr>
<td>3.</td>
<td>The prescriber communicates with other professionals to obtain collateral history and collaborate in the monitoring of outcome and side effects during the medication trial.</td>
</tr>
<tr>
<td>4.</td>
<td>The prescriber develops a psychosocial and psychopharmacological treatment plan based upon the best available evidence.</td>
</tr>
<tr>
<td>5.</td>
<td>The prescriber develops a plan to monitor the patient during the medication trial.</td>
</tr>
<tr>
<td>6.</td>
<td>The prescriber is cautious when the medication trial cannot be appropriately monitored.</td>
</tr>
<tr>
<td>7.</td>
<td>The prescriber educates the patient and family about the patient’s diagnosis and treatment plan.</td>
</tr>
<tr>
<td>8.</td>
<td>The prescriber obtains and documents informed consent before initiating the medication trial and at appropriate intervals during the trial.</td>
</tr>
<tr>
<td>9.</td>
<td>The informed consent process focuses on the risks and benefits of the proposed and alternative treatments.</td>
</tr>
<tr>
<td>10.</td>
<td>The medication trial should involve an adequate dose of medication for an adequate duration.</td>
</tr>
<tr>
<td>11.</td>
<td>The prescriber reassesses the patient if the patient fails to respond to the medication trial as expected.</td>
</tr>
<tr>
<td>12.</td>
<td>The prescriber has a clear rationale for using medication combinations.</td>
</tr>
<tr>
<td>13.</td>
<td>The prescriber has a specific plan for medication discontinuation.</td>
</tr>
</tbody>
</table>


**Table 21-2** Target Symptom Approach to Psychopharmacologic Management

<table>
<thead>
<tr>
<th>Target Symptom</th>
<th>Medication Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation</td>
<td>Atypical antipsychotic</td>
</tr>
<tr>
<td></td>
<td>Typical antipsychotic</td>
</tr>
<tr>
<td></td>
<td>Antipsychotic</td>
</tr>
<tr>
<td></td>
<td>Anxiolytic (e.g., benzodiazepine)</td>
</tr>
<tr>
<td>Aggression</td>
<td>Stimulant</td>
</tr>
<tr>
<td></td>
<td>Atypical antipsychotic</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Antidepressant</td>
</tr>
<tr>
<td></td>
<td>Anxiolytic</td>
</tr>
<tr>
<td>Depression</td>
<td>Antidepressant</td>
</tr>
<tr>
<td>Hyperactivity, inattention, impulsivity</td>
<td>Stimulant</td>
</tr>
<tr>
<td></td>
<td>Atomoxetine</td>
</tr>
<tr>
<td></td>
<td>Alpha-agonist</td>
</tr>
<tr>
<td>Mania</td>
<td>Atypical antipsychotic</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Atypical antipsychotic</td>
</tr>
</tbody>
</table>

Bibliography


<table>
<thead>
<tr>
<th>NAME</th>
<th>FDA APPROVED (AGE RANGE IN YEARS)</th>
<th>TARGET SYMPTOMS</th>
<th>USUAL DAILY DOSAGE RANGE</th>
<th>SUGGESTED TOP END OF DAILY DOSAGE RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STIMULANTS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Long Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylphenidate (Concerta)</td>
<td>ADHD (6 and up)</td>
<td>Inattention</td>
<td>6-12: 18-54 mg</td>
<td>6-12: 54 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperactivity</td>
<td>&gt;12: 18-72 mg</td>
<td>&gt;12: 72 mg</td>
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<tr>
<td></td>
<td></td>
<td>Impulsivity</td>
<td></td>
<td></td>
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<td>ADHD (6 and up)</td>
<td>Inattention</td>
<td>Child: 5-30 mg</td>
<td>Child: 30 mg</td>
</tr>
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<td></td>
<td></td>
<td>Hyperactivity</td>
<td></td>
<td></td>
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<tr>
<td>Amphetamine combination (Adderall XR)</td>
<td>ADHD (6 and up)</td>
<td>Inattention</td>
<td>6-12: 5-10 mg</td>
<td>6-12: 30 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperactivity</td>
<td>&gt;12: 10-20 mg</td>
<td>&gt;12: 40 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Impulsivity</td>
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<tr>
<td>Dextroamphetamine (Dexedrine Spansule)</td>
<td>ADHD (6 and up)</td>
<td>Inattention</td>
<td>5-40 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperactivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intermediate Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Methylphenidate (Metadate CD, Metadate ER, Ritalin LA, Ritalin SR)</td>
<td>ADHD (6 and up)</td>
<td>Inattention</td>
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</tr>
<tr>
<td></td>
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<td>Hyperactivity</td>
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<td>Dexmethylphenidate (Focalin)</td>
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<td>20 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperactivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylphenidate (Ritalin, Methylin)</td>
<td>ADHD (6 and up)</td>
<td>Inattention</td>
<td>5-30 mg</td>
<td>60 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperactivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphetamine combination (Adderall)</td>
<td>ADHD (3 and up)</td>
<td>Inattention</td>
<td>3-5: 2.5-40 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperactivity</td>
<td>&gt;6: 5-40 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Impulsivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dextroamphetamine (Dexedrine)</td>
<td>ADHD (6 and up)</td>
<td>Inattention</td>
<td>2.5-40 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperactivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITOR</strong></td>
<td>ADHD (6 and up)</td>
<td>Inattention</td>
<td>&lt;7 kg: 0.5-1.2 mg/kg</td>
<td>&lt;70 kg: 1.4 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperactivity</td>
<td>&gt;70 kg: 40-80 mg</td>
<td>&gt;70 kg: 100 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Impulsivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atomoxetine (Strattera)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>α-AGONISTS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine (Catapres)</td>
<td>Not approved for ADHD in children &amp; adolescents</td>
<td>Inattention</td>
<td>27-40.5 kg: 0.05-0.2 mg</td>
<td>27-40.5 kg: 0.2 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperactivity</td>
<td>40.5-45 kg: 0.05-0.3 mg</td>
<td>40.5-45 kg: 0.3 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Impulsivity</td>
<td>&gt;45 kg: 0.05-0.4 mg</td>
<td>&gt;45 kg: 0.4 mg</td>
</tr>
<tr>
<td>Clonidine (Kapvay)</td>
<td>ADHD (6-17)</td>
<td>Inattention</td>
<td>0.1-0.4 mg/day</td>
<td>0.4 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperactivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guanfacine (Tenex)</td>
<td>Not approved for ADHD in children &amp; adolescents</td>
<td>Inattention</td>
<td>27-40.5 kg: 0.5-2 mg</td>
<td>27-40.5 kg: 2 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperactivity</td>
<td>40.5-45 kg: 0.5-3 mg</td>
<td>40.5-45 kg: 3 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Impulsivity</td>
<td>&gt;45 kg: 0.5-4 mg</td>
<td>&gt;45 kg: 4 mg</td>
</tr>
<tr>
<td>Guanfacine (Intuniv)</td>
<td>ADHD (6-17)</td>
<td>Inattention</td>
<td>1-4 mg</td>
<td>4 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperactivity</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADHD, attention-deficit/hyperactivity disorder.
or malaise associated with chronic physical illnesses. There is a range of stimulant options, including those with short half-lives (typically 4 hr) and those with long half-lives (8-12 hr). The most commonly reported side effects are appetite suppression and sleep disturbances. Nervousness, headaches, abdominal pain, dizziness, palpitations, tachycardia have also been reported. More serious reactions include psychosis, mania, hypertension, dependency, and abuse. Anorexia and weight loss have been noted with controversy about their impact on ultimate height attainment.

Sudden death has been reported in association with the use of stimulants in children, although a large study did not find an increased rate of serious cardiac events. Currently, no routine pretreatment cardiology evaluation is indicated unless the patient has a structural cardiac abnormality and/or cardiac-related symptoms; in this situation, cardiology clearance is recommended.

Atomoxetine is a selective inhibitor of presynaptic norepinephrine transporters; it increases dopamine and norepinephrine in the prefrontal cortex. It is effective in treating ADHD for 24 hr despite a plasma half-life of 4 hr. Common side effects include headache, abdominal pain, insomnia, somnolence, erectile dysfunction, irritability, fatigue, weight loss, and dizziness along with nonclinical increases in heart rate and blood pressure. More serious reactions include psychosis, mania, aggressive behavior, suicidal ideation, depression, seizures, and hepatotoxicity.

The α-adrenergic agents (clonidine and guanfacine) are presynaptic adrenergic agonists that appear to stimulate inhibitory presynaptic autoreceptors in the central nervous system. These medications (see Table 21-5) have moderate evidence for the treatment of ADHD and ADHD with oppositional defiant disorder, and weak evidence for the treatment of agitation in autism. Two longer-acting preparations of each agent (Kapvay and Intuniv) have recently received FDA approval for use in ADHD. Sedation, hypotension, dry mouth, depression, and confusion are potential side effects. Abrupt withdrawal can result in rebound hypertension. Guanfacine appears to be less sedating and to have a longer duration of action than clonidine.

**ANTIDEPRESSANTS**

Antidepressant drugs act on pre- and postsynaptic receptors affecting the release and reuptake of brain neurotransmitters, including norepinephrine, serotonin, and dopamine (Table 21-4). There is strong evidence for the effectiveness of antidepressant medications in the treatment of anxiety and obsessive-compulsive disorders (NNT approximates 3 and 6, respectively), and weaker evidence for the treatment of depressive disorders (NNT approximates 10). Suicidal

<table>
<thead>
<tr>
<th>NAME</th>
<th>FDA APPROVED (AGE RANGE IN YEARS)</th>
<th>TARGET SYMPTOMS</th>
<th>USUAL DAILY DOSAGE RANGE</th>
<th>SUGGESTED TOP END OF DAILY DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SELECTIVE SEROTONIN REUPTAKE INHIBITORS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram (Celexa)</td>
<td>Not approved for anxiety &amp; depression in children &amp; adolescents</td>
<td>Depression Anxiety Obsessions/compulsions</td>
<td>20-40 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>Escitalopram (Lexapro)</td>
<td>Depression (12-17)</td>
<td>Depression Anxiety Obsessions/compulsions</td>
<td>10-20 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>Fluoxetine (Prozac)</td>
<td>Depression (8-17) OCD (7-17)</td>
<td>Depression Anxiety Obsessions/compulsions</td>
<td>10-60 mg</td>
<td>60 mg</td>
</tr>
<tr>
<td>Sertraline (Zoloft)</td>
<td>OCD (6-17)</td>
<td>Depression Anxiety Obsessions/compulsions</td>
<td>25-200 mg</td>
<td>200 mg</td>
</tr>
<tr>
<td><strong>TRICYCLIC ANTIDEPRESSANTS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clomipramine (Anafranil)</td>
<td>OCD (10-17)</td>
<td>Obsessions/compulsions</td>
<td>25-100 mg</td>
<td>Lesser of 200 mg or 3 mg/kg</td>
</tr>
<tr>
<td><strong>ATYPICAL ANTIDEPRESSANTS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion (Wellbutrin XL)</td>
<td>Not approved for depression in children &amp; adolescents</td>
<td>Depression</td>
<td>150-300 mg</td>
<td>450 mg</td>
</tr>
<tr>
<td>Venlafaxine (Effexor XR)</td>
<td>Not approved for anxiety &amp; depression in children &amp; adolescents</td>
<td>Depression Anxiety</td>
<td>75-225 mg</td>
<td>225 mg</td>
</tr>
<tr>
<td><strong>ANXIOLYTIC AGENTS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>Not approved for anxiety</td>
<td>Anxiety</td>
<td>0.5-6 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>Not approved for panic in children &amp; adolescents</td>
<td>Panic</td>
<td>0.5-1 mg</td>
<td>4 mg</td>
</tr>
<tr>
<td>Buspirone (BuSpar)</td>
<td>Not approved for anxiety &amp; depression in children &amp; adolescents</td>
<td>Anxiety</td>
<td>15-30 mg</td>
<td>60 mg</td>
</tr>
<tr>
<td>Hydroxyzine (Atarax, Vistaril)</td>
<td>Anxiety</td>
<td>Anxiety</td>
<td>50 mg &gt;6: 50-100 mg</td>
<td>&lt;6: 2 mg/kg</td>
</tr>
</tbody>
</table>

ADHD: attention-deficit/hyperactivity disorder; OCD: obsessive-compulsive disorder.
thoughts have been reported during treatment with all antidepressant medications. The overall risk difference during suicidal ideation/Attempts across all randomized controlled antidepressant trials and indications has been reported to be 0.7%, corresponding to a number needed to harm of 143.

The selective serotonin reuptake inhibitors (SSRIs), which, as their name suggests, inhibit the reuptake of serotonin, have a large margin of safety with no appreciable cardiovascular effects. Side effects include irritability, insomnia, appetite changes, gastrointestinal symptoms, headache, diaphoresis, restlessness, behavioral activation, and sexual dysfunction. Withdrawal symptoms are more common in short-acting SSRIs (sertraline, citalopram, escitalopram), leading to a recommendation for divided doses if these medications are used.

The tricyclic antidepressants (TCAs) have mixed mechanisms of action (e.g., clomipramine is primarily serotonergic; imipramine is both noradrenergic and serotonergic). With the advent of the SSRIs, this class has relatively strong antagonistic activity (5-HT 2 ) agents (Table 21-5). Based on their mechanism of action, antipsychotic medications can be divided into typical (blocking dopamine D2 receptors) and atypical (mixed dopaminergic and serotonergic [5-HT2] activity) agents (Table 21-5).

The atypical antipsychotics have relatively strong antagonistic interactions with 5-HT2 receptors and perhaps more variable activity at central adrenergic, cholinergic, and histaminic sites, which might account for varying side effects noted among these agents. These medications have strong evidence for the treatment of agitation in autism (NNT approximates 2-7), and for the treatment of schizophrenia (NNT approximates 4-10), bipolar disorder (NNT approximates 3-4), and aggression (NNT approximates 2-5). Risperidone and aripiprazole are 2 of the most well-studied and commonly used medications in this class.

The atypical antipsychotics have significant side effects including extrapyramidal symptoms (e.g., restlessness and dyskinesias), weight gain, metabolic syndrome, diabetes, hyperlipidemia, hyperprolactinemia, hematologic adverse effects (e.g., leukopenia or neutropenia), seizures, hepatotoxicity, neuroleptic malignant syndrome, and cardiovascular effects. For all atypical antipsychotics, body mass index, blood pressure, fasting blood glucose, fasting lipid profiles, and abnormal movements should be closely monitored. If there is a family or personal history suggestive of cardiac disease, electrocardiograms should also be monitored.
There are special considerations in the use of psychotropic medications. Because of their limited evidence of effectiveness and concerns about safety, mood stabilizer medications (Table 21-6) have limited use in the treatment of child and adolescent psychiatric disorders. For the treatment of bipolar mania in adolescents, atypical antipsychotics are considered first-line therapy. Medications with high baseline rates of liver clearance (e.g., haloperidol, sertraline, venlafaxine, TCAs) are significantly affected by hepatic disease. For drugs that have significant hepatic metabolism, intravenous administration may be preferred because parenteral administration avoids first-pass liver metabolic effects and the dosing and action of parenteral medications are similar to those in patients with normal hepatic function. Valproic acid can impair the metabolism of the hepatocyte disproportionate to the degree of hepatocellular damage. In patients with valproate-induced liver injury, low albumin, high prothrombin, and high ammonia may be seen without significant elevation in liver transaminases.

Medications with anticholinergic side effects can slow gastrointestinal motility, affecting absorption and causing constipation. SSRIs increase gastric motility and can cause constipation. SSRIs have the potential to increase the risk of gastrointestinal bleeding, especially when they are co-administered with nonsteroidal anti-inflammatory drugs. Extended-release or controlled-release preparations of medications can reduce gastrointestinal side effects, particularly where gastric distress is related to rapid increases in plasma drug concentrations.

### Kidney Disease

With the exceptions of lithium and gabapentin, psychotropic medications do not generally require significant dosing adjustments in kidney failure. It is important to monitor serum concentrations in renal insufficiency, particularly for medications with a narrow therapeutic index; cyclosporine can elevate serum lithium levels by decreasing lithium excretion. Patients with kidney failure and those on dialysis appear to be more sensitive to TCA side effects, possibly because of the accumulation of hydroxylated tricyclic metabolites.

### Hepatic Disease

Lower doses of medications may be required in patients with hepatic disease. Initial dosing of medications should be reduced and titration should proceed slowly. In steady-state situations, changes in protein binding can result in elevated unbound medication, resulting in increased drug action even in the presence of normal serum drug concentrations. Because it is often difficult to predict changes in protein binding, it is important to maintain attention to the clinical effects of psychotropic medications and not rely exclusively on serum drug concentrations.

In acute hepatitis, there is generally no need to modify dosing because metabolism is only minimally altered. In chronic hepatitis and cirrhosis, hepatocytes are destroyed and doses may need to be modified.

Medications with high baseline rates of liver clearance (e.g., haloperidol, sertraline, venlafaxine, TCAs) are significantly affected by hepatic disease. For drugs that have significant hepatic metabolism, intravenous administration may be preferred because parenteral administration avoids first-pass liver metabolic effects and the dosing and action of parenteral medications are similar to those in patients with normal hepatic function. Valproic acid can impair the metabolism of the hepatocyte disproportionate to the degree of hepatocellular damage. In patients with valproate-induced liver injury, low albumin, high prothrombin, and high ammonia may be seen without significant elevation in liver transaminases.

### MOOD STABILIZERS

Because of their limited evidence of effectiveness and concerns about safety, mood stabilizer medications (Table 21-6) have limited use in the treatment of child and adolescent psychiatric disorders. For the treatment of bipolar mania in adolescents, atypical antipsychotics are considered first-line therapy.

Lithium’s mechanism of action is not well understood; proposed theories relate to neurotransmission, endocrine effects, circadian rhythm, and cellular processes. Common side effects include polyuria and polydipsia and central nervous system symptoms (tremor, somnolence, and memory impairment). Periodic monitoring of lithium levels along with thyroid and renal function is needed. Lithium serum levels of 0.8-1.2 mEq/L are targeted for acute episodes and 0.6-0.9 mEq/L are targeted for maintenance therapy.

Valproic acid is an anticonvulsant with a therapeutic plasma concentration range of 50-100 µg/mL. Common side effects include sedation, gastrointestinal symptoms, and hair thinning. Idiosyncratic bone marrow suppression and liver toxicity have been reported, necessitating monitoring of blood counts as well as liver and kidney function.

### MEDICATION USE IN PHYSICAL ILLNESS

There are special considerations in the use of psychotropic medications with physically ill children. Between 80% and 95% of psychotropic medications are protein bound, with the exceptions being lithium (0%), methylphenidate (10-30%), venlafaxine (25-30%), gabapentin (0-3%), and topiramate (9-17%). As a result, psychotropic levels may be directly affected because albumin binding is reduced in many physical illnesses. Metabolism is primarily through the liver and gastrointestinal tract, with excretion via the kidney. Therefore, dosages may need to be adjusted in children with hepatic or renal impairment.

### Haloperidol

Haloperidol is a high-potency butyrophenone that is the typical antipsychotic most commonly used. This medication is useful in psychosis, Tourette disorder, and severe agitation. Side effects include anticholinergic effects, weight gain, drowsiness, and extrapyramidal symptoms (dystonia, rigidity, tremor, and akathisia). There is a risk of tardive dyskinesia (see Chapter 597.3) with chronic administration.

### Table 21-6 Medications for Mania

<table>
<thead>
<tr>
<th>MOOD STABILIZERS</th>
<th>FDA APPROVED (AGE RANGE IN YEARS)</th>
<th>TARGET SYMPTOMS</th>
<th>USUAL DAILY DOSAGE RANGE</th>
<th>SUGGESTED TOP END OF DAILY DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium carbonate (Eskalith, Eskalith CR, Lithobid)</td>
<td>Bipolar disorder (12-17)</td>
<td>Mania</td>
<td>&lt;22 kg: 600 mg</td>
<td>1800 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Depression</td>
<td>22-41 kg: 900 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;41 kg: 1200 mg</td>
<td></td>
</tr>
<tr>
<td>Divalproex (Depakote, Depakote ER)</td>
<td>Not approved for mania in children &amp; adolescents</td>
<td>Mania</td>
<td>Teen: 10-60 (Blood valproic acid level 50-100 µg/mL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>60 mg/kg</td>
<td></td>
</tr>
<tr>
<td>ATYPICAL ANTIPSYCHOTICS</td>
<td>Bipolar disorder (10-17)</td>
<td>Irritability</td>
<td>2-30 mg</td>
<td>30 mg Autism: 15 mg</td>
</tr>
<tr>
<td>Aripiprazole (Abilify)</td>
<td>Schizophrenia (13-17)</td>
<td>Psychosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Irritability in autism (6-17)</td>
<td>Mania</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mania</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Risperidone (Risperdal)</td>
<td>Psychosis</td>
<td>0.5-6 mg</td>
<td>Bipolar &amp; Schizophrenia: 6 mg</td>
</tr>
<tr>
<td></td>
<td>Bipolar disorder (10-17)</td>
<td>Mania</td>
<td>15-20 kg: 0.25 mg-0.5 mg</td>
<td>Autism: 3 mg</td>
</tr>
<tr>
<td></td>
<td>Schizophrenia (13-17)</td>
<td>Mania</td>
<td>&gt;20 kg: 0.5-1 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Irritability in autism (5-17)</td>
<td>Mania</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aggression</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Agitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Irritability</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Because most psychotropic medications are highly protein-bound, they are not significantly cleared by dialysis. Lithium, gabapentin, and topiramate are essentially completely removed by dialysis, and the common practice is to administer these medications after dialysis. Patients on dialysis often have significant fluid shifts and are at risk for dehydration, with neuroleptic malignant syndrome being more likely in these situations.

**Heart Disease**
Cardiovascular effects of psychotropic medications can include orthostatic hypotension, conduction disturbances, and arrhythmias. Orthostatic hypotension is one of the most common cardiovascular side effects of TCAs. Trazodone can cause orthostatic hypotension and exacerbate myocardial instability; SSRIs and bupropion are preferred as antidepressant agents in patients with heart disease.

There is the potential for increased morbidity and mortality in patients with preexisting cardiac conduction problems. Some of the calcium channel-blocking agents (e.g., verapamil) can slow atrioventricular conduction and can theoretically interact with a TCA. Patients with Wolff-Parkinson-White syndrome (see Chapter 435.3) who have a short PR interval (<0.12 sec) and widened QRS interval associated with paroxysmal tachycardia are at high risk for life-threatening ventricular tachycardia that may be exacerbated by the use of a TCA. Quinidine-like effects of TCAs and the antipsychotic agents can lead to prolongation of the QTc interval, with increased risk of ventricular tachycardia and ventricular fibrillation, particularly in patients with structural heart disease. Patients with a baseline QTc interval of >440 msec should be considered at particular risk. The range of normal QTc values in children is 400 msec ± 25-30 msec. A QTc value that exceeds 2 SD (450-460 msec) is considered too long and may be associated with increased mortality. An increase in the QTc from baseline of >60 msec is also associated with increased mortality.

**Respiratory Disease**
Anxiolytic agents can increase the risk of respiratory suppression in patients with pulmonary disease. SSRIs and bupropion are good alternative medications for treating anxiety. Consideration should be given to possible airway compromise due to acute laryngospasm when dopamine-blocking agents such as antipsychotic or antiepileptic medications are used.

**Neurologic Disease**
Psychotropic medications can be used safely with epilepsy following consideration of potential interactions between the psychotropic medication, the seizure disorder, and the anticonvulsant medication. Any behavioral toxicity of anticonvulsants used either alone or in combination should be considered before proceeding with psychotropic treatment. Simplification of combination anticonvulsant therapy or a change to another agent can result in a reduction of behavioral or emotional symptoms and obviate the need for psychotropic intervention. Clomipramine and bupropion possess significant seizure-inducing properties and should be avoided when the risk of seizures is present.

**Neuroleptic Malignant Syndrome**
*Neuroleptic malignant syndrome* is a rare and potentially fatal reaction that can occur during treatment with antipsychotic agents (see Chapter 176). The syndrome generally manifests with fever, muscle rigidity, autonomic instability, and delirium. It is associated with elevated serum creatine phosphokinase levels, a metabolic acidosis, and high end-tidal CO₂ excretion. It has been estimated to occur in 0.2-1% of patients treated with dopamine-blocking agents. Malnutrition and dehydration in the context of an organic brain syndrome and simultaneous treatment with lithium and antipsychotic agents can increase the risk. Mortality rates may be as high as 20-30% as a result of dehydration, aspiration, kidney failure, and respiratory collapse. Differential diagnosis of neuroleptic malignant syndrome includes infections, heat stroke, malignant hyperthermia, lethal catatonia, agitated delirium, thyrotoxicosis, serotonin syndrome, drug withdrawal, and anticholinergic or amphetamine, ecstasy, salicylate toxicity.

**Serotonin Syndrome**
Serotonin syndrome is characterized by a triad of mental status changes, autonomic hyperactivity, and neuromuscular abnormalities (see Chapter 63). It is the result of an excess agonism of the central and peripheral nervous system serotonin receptors and can be caused by a range of drugs including SSRIs, valproate, and lithium. Drug-drug interactions that can cause serotonin syndrome include linezolid (an antibiotic that has monoamine oxidase inhibitor properties) and anti-migraine preparations used with an SSRI, as well as combinations of SSRIs, trazodone, bupropine, and venlafaxine. It is generally self-limited and can resolve spontaneously after the serotonergic agents are discontinued. Severe cases require the control of agitation, autonomic instability, and hyperthermia as well as the administration of 5-HT₂A antagonists (e.g., cyproheptadine).

Bibliography is available at Expert Consult.

### 21.2 Psychotherapy

**David R. DeMaso and Heather J. Walter**

Psychotherapy in children may also be effective in reducing patient symptomatology. Effect sizes in research studies range from 0.71 to 0.84, which are as large as or larger than the effects of psychiatric medications or medicines for many physical illnesses. Despite benefit, only a minority of patients achieve the same level of functioning as average children, because in community settings the effect size of psychotherapy approaches zero. This poor response might reflect the fact that treatment in real-world community settings involves complex and co-occurring disorders, as opposed to the research or academic setting, where comorbid conditions are often excluded.

A variety of psychotherapeutic approaches exist with varying levels of evidence regarding their effectiveness. Differences between therapeutic approaches may be less pronounced in practice than in theory. The quality of the therapist–patient alliance consistently has been shown to be the strongest predictor of treatment outcome. A positive therapeutic relationship, expecting change to occur, facing problems assertively, increasing mastery, and attributing change to the participation in the therapy have all been connected to effective therapy.

The use of psychotherapy involves a series of interconnected steps including performing an assessment, deciding upon treatment and a monitoring plan, obtaining treatment assent or consent, and implementing treatment. Cognitive, emotional, and/or behavioral symptoms are identified that become the targets for evidence-based psychotherapeutic interventions. Psychotherapists ideally develop a treatment plan by combining known evidence-based practices about specific interventions with their clinical judgment to arrive at a specific intervention plan for the individual patient. It is not unusual for the psychotherapist to use elements from more than one treatment approach, including psychopharmacology.

**BEHAVIOR THERAPY**

Behavior therapy is based upon both classic (pavlovian) and operant (skinnerian) conditioning. Both of these approaches do not concern themselves with the inner motives of the individual, but instead address the antecedent stimuli and consequent responses. The treatment begins with a behavioral assessment with interview, observation, diary, and rating scale components, along with a functional analysis of the setting context, immediately preceding external events, and real-world consequences of the behavior. A treatment plan is then developed to modify the maladaptive functions of the behavior, using tools such as positive and negative reinforcement, social and tangible rewards, shaping, modeling, and prompting to increase positive behavior, and extinction, stimulus control, punishment, response cost, overcorrection, differential reinforcement of incompatible behavior, graded exposure/
Bibliography


systematic desensitization, flooding, modeling, and role playing to decrease negative behavior.

Behavior therapy has shown applicability to anxiety disorders, obsessive-compulsive and related disorders, posttraumatic stress disorder, behavior disorders, ADHD, nocturnal enuresis, autism spectrum disorder, and intellectual disability.

COGNITIVE-BEHAVIORAL THERAPY
Cognitive-behavioral therapy (CBT) is based on social and cognitive learning theories and extends behavior therapy to address the influence of cognitive processes on behavior. These cognitive processes include social information processing (automatic and controlled), fixed patterns of thinking or beliefs (cognitive schema), and emotional effects mediating cognitive attributions and behavior. CBT is problem-oriented treatment that seeks to identify and change cognitive distortions (e.g., learned helplessness or irrational fears), identify and avoid distressing situations, and identify and practice distress-reducing behavior. Self-monitoring (daily thought record), self-instruction (brief sentences asserting thoughts that are comforting and/or adaptive), and self-reinforcement (rewarding oneself) are key tools used to facilitate achievement of the CBT treatment goals.

CBT has shown applicability to the treatment of behavior, depressive, and anxiety disorders. Specially modified versions of CBT have shown applicability to the treatment of other disorders. Trauma-focused CBT involves a combination of psychoeducation, teaching effective relaxation, affective modulation, and cognitive coping and processing skills, engaging in a trauma narrative, mastering trauma reminders, and enhancing future safety and development, and is considered the first-line treatment for posttraumatic stress disorder. Dialectical behavioral therapy combines standard CBT with concepts of distress tolerance, emotional regulation, interpersonal effectiveness, and mindfulness drawn from Buddhist meditative practice. Dialectical behavioral therapy has shown promise for the treatment of borderline personality disorder, bipolar disorder, suicidal behavior, and other manifestations of emotional and behavioral dysregulation.

FAMILY THERAPY
Although family therapy covers a broad range of approaches, the core idea in family therapy is that the cause of problems in individuals is thought to lie in patterns of family interaction, with other family members helping to maintain the problem. Family dysfunction can take a variety of forms, including enmeshment, disengagement, role-reversal or confusion, and maladaptive communication patterns. Family therapy begins with an assessment of the family system, including observing patterns of interaction, assessing family beliefs and the meanings attached to behaviors, defining social and cultural contexts, exploring the presenting problem in the context of individual and family development, assessing the family’s style of dealing with problems, and identifying family strengths and weaknesses. Family therapy techniques are drawn from 2 major theoretical models: structural and behavioral. Structural family therapy develops capacities believed to foster well-functioning families, including clear and flexible boundaries between individuals, well-defined roles, and an appropriate balance between closeness and independence. Behavioral family therapy focuses on behavioral sequences that occur in daily life, and attempts to interrupt unhelpful patterns and strengthen positive patterns through effective communication and problem solving.

Family therapy has shown applicability to anorexia and substance abuse, and for these disorders is the treatment of choice. For other disorders (e.g., depressive, anxiety, obsessive-compulsive, and behavior), the evidence is more limited.

PSYCHODYNAMIC PSYCHOTHERAPY
At the core of psychodynamic psychotherapy lies a dynamic interaction between different parts or aspects of the mind. This approach is based on the belief that much of one’s mental activity occurs outside one’s awareness. The patient is often unaware of internal conflicts because threatening or painful emotions, impulses, and memories are repressed. Behavior is then controlled by what the patient does not know about himself or herself. Therapy objectives are to increase self-understanding, increase acceptance of feelings, shift to mature defense mechanisms, and develop realistic relationships between self and others. This therapy is nondirective to allow the patient’s characteristic patterns to emerge so that self-understanding and a corrective emotional experience can then be fostered by the therapist.

Psychodynamic psychotherapy has shown applicability for the treatment of emotional problems (e.g., anxiety, depression) as well as maladaptive aspects of personality. Limited applicability has been shown for behavior, eating, and trauma-related disorders. Brief, time-limited psychodynamic psychotherapy can be appropriate for youth who are in acute situational distress, while long-term therapy can be appropriate when the biological or social factors destabilizing the child’s adaptation and development are chronic, or the psychological difficulties due to comorbidities are complex, or entrenched conflicts and developmental interferences are present.

SUPPORTIVE PSYCHOTHERAPY
Supportive psychotherapy aims to minimize levels of emotional distress through the provision of individual and contextual support. Treatment is focused on the here and now. The therapist is active and helpful in providing the patient with symptomatic relief by containing anxiety, sadness, and anger. The therapist provides education and encouragement to bolster a patient’s existing coping mechanisms. The therapist also facilitates problem solving and social and instrumental support for contextual symptom-generating problems.

PARENTING INTERVENTIONS
Parenting interventions are based upon attachment and social learning theory. Attachment theory proposes that the quality of care provided to the child, particularly sensitivity and responsiveness, leads to a secure or insecure attachment, which in turn influences the development of internal working models of self and others. A history of consistent and sensitive care by a parent is expected to lead to the child developing a model of self as lovable and others as loving and helpful. Social learning theory hypothesizes that children’s real-life experiences and exposures directly or indirectly shape behavior, and that new positive experiences and exposures can change behavior favorably.

Parenting interventions seek to address both attachment and social learning deficits by improving both the parent–child relationship and parenting skills. Core attachment skills include spending quality time with the child, increasing verbal interaction, showing physical affection, providing contingent praise, and engaging in child-directed play. Core parenting skills include increasing reinforcement of positive behaviors, decreasing reinforcement of negative behaviors, applying consequences for dangerous/destructive behavior, and making parental response predictable, contingent, and immediate.

Parenting interventions have shown applicability for the behavior disorders and ADHD.

Bibliography is available at Expert Consult.

21.3 Psychiatric Hospitalization

David R. DeMaso and Heather J. Walter

Psychiatric hospital programs are meant to address the serious risks and severe impairments caused by the most acute and complex forms of psychiatric disorder that cannot be managed effectively at any other level of care. Their goal is to produce rapid clinical stabilization that allows an expeditious, safe, and appropriate treatment transition to a less-intensive level of mental healthcare outside of the hospital.

High levels of illness severity combined with significant functional impairment signal a need for hospitalization. Admission criteria must include significant signs and symptoms of active psychiatric disorder(s). Functional admission indicators generally include a significant risk of self-harm and/or harm to others, although in some cases the patient is unable to meet basic self-care or healthcare needs, jeopardizing
Bibliography
well-being. Serious emotional disturbances that prevent participation in family, school, or community life can also rise to a level of global impairment that can only be addressed on an inpatient basis.

_DischARGE planning_ begins at the time of admission, when efforts are made to coordinate care with services and resources that are already in place for the child or adolescent in the community. Step-down care might be needed in partial hospital or residential settings if integrated services in a single location remain indicated after sufficient clinical stabilization has occurred in the hospital setting. Transition from the hospital entails active collaboration and communication with pediatric practitioners in the child’s medical home.

_Bibliography is available at Expert Consult._
Bibliography
Chapter 22

Somatic Symptom and Related Disorders

Patricia I. Ibeziako and David R. DeMaso

Pediatric psychosomatic medicine deals with the relation between physiologic and psychological factors in the causation or maintenance of disease states. The process whereby distress is experienced and/or expressed in physical symptoms is referred to as somatization or psychosomatic illness. Even though somatic symptoms are present in virtually every psychiatric disorder, they are most prominent in the various somatic symptom disorders.

In the Diagnostic Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), illnesses previously referred to as somatoform disorders are defined as somatic symptom disorders. Somatic symptom disorders are classified on the basis of distressing physical symptoms and excessive thoughts, feelings or behaviors in relation to these symptoms rather than the absence of a medical explanation for somatic symptoms. These disorders form a continuum that can range from pain to disabling neurological symptoms and they generally interfere with school, home life and peer relationships. The DSM-5 Somatic Symptom and Related Disorders category includes the following disorders related to children and adolescents: conversion disorder (or functional neurologic symptom disorder), somatic symptom disorder, factitious disorder, psychological factors affecting other medical conditions, and other specified/unspecified somatic symptom disorders (Tables 22-1 through 22-5 identify the DSM-5 diagnostic criteria).

Multiple terms used to describe somatic symptom disorders include “functional,” “psychosomatic,” or “medically unexplained symptoms.” Additionally, most patients are seen by general practitioners and specialists and may receive specialty-specific syndrome diagnoses such as visceral hyperalgesia, irritable bowel syndrome, chronic fatigue syndrome, or noncardiac chest pain. The diagnostic heterogeneity that exists across the different medical specialists contributes to the different diagnostic labels. Studies indicate a significant overlap in the symptoms and presentation of patients with somatic symptoms who have received different diagnoses from different specialties.

Moreover, functional syndromes share similarities in etiology, pathophysiology, neurobiology, psychological mechanisms, patient characteristics, and management and treatment response, which is indicative of a single spectrum of disorders. It is helpful for healthcare providers to avoid the dichotomy of approaching illness using a medical model in which diseases are considered as being either organic or psychological.
Part III  Behavioral and Psychiatric Disorders

Table 22-4  DSM-5 Diagnostic Criteria for Factitious Disorders

Factitious Disorder Imposed on Self
A. Falsification of physical or psychological signs or symptoms, or induction of injury or disease, associated with identified deception.
B. The individual presents himself or herself to others as ill, impaired, or injured.
C. The deceptive behavior is evident even in the absence of obvious external rewards.
D. The behavior is not better explained by another mental disorder, such as delusional disorder or another psychotic disorder.

Factitious Disorder Imposed on Another (Previously Factitious Disorder by Proxy)
A. Falsification of physical or psychological signs or symptoms, or induction of injury or disease, in another, associated with identified deception.
B. The individual presents another individual (victim) to others as ill, impaired, or injured.
C. The deceptive behavior is evident even in the absence of obvious external rewards.
D. The behavior is not better explained by another mental disorder, such as delusional disorder or another psychotic disorder.

Note: The perpetrator, not the victim, receives this diagnosis.

Table 22-5  DSM-5 Diagnostic Criteria for Other Specified/Unspecified Somatic Symptom and Related Disorders

Other Specified
This category applies to presentations in which symptoms characteristic of a somatic symptom and related disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet full criteria for any of the disorders in the somatic symptom and related disorders diagnostic class. Examples of presentations that can be specified using the “other specified” designation include the following:
1. Brief somatic symptom disorder: Duration of symptoms <6 mo.
2. Brief illness anxiety disorder: Duration of symptoms <6 mo.
3. Illness anxiety disorder without excessive health-related behaviors: Criterion D for illness anxiety disorder is not met.
4. Pseudocyesis: A false belief of being pregnant that is associated with objective signs and reported symptoms of pregnancy.

Unspecified
This category applies to presentations in which symptoms characteristic of a somatic symptom and related disorder that cause clinically significant distress or impairment in functioning predominate but do not meet criteria for any of the other disorders in the somatic symptom and related disorders diagnostic class.

or psychologically based. In contrast, a biobehavioral continuum of disease characterizes illness as occurring across a spectrum ranging from a biologic etiology on one end to predominantly a psychosocial etiology on the other.

Epidemiology
Between 10% and 30% of children worldwide experience physical symptoms that are described as “functional” or unexplained by a physical illness. Estimated prevalence varies greatly between studies based on the type of symptoms and the study methodology. The frequency and heterogeneity of complaints increase with age with symptoms occurring more frequently in females.

The majority of children with persistent complaints of abdominal pain meet criteria for functional abdominal pain or somatic symptom disorder with predominant pain in DSM-5. In a prospective study, patients with functional abdominal pain carry long-term vulnerability to anxiety that begins in childhood and persists into late adolescence and early adulthood, even if abdominal pain resolves.

Headaches, back pain, limb pain and chest pain, as well as other gastrointestinal symptoms, are also frequently occurring pain symptoms in adolescents. Prevalence rates of conversion disorder in adolescents are 0.3-10%. Nonepileptic seizures, loss of consciousness, and motor conversion symptoms are common somatic neurologic complaints across cultures.

Risk Factors
Family and Environmental
Genetic
A possible genetic etiology in somatization disorders is suggested by findings of a 29% concordance rate in monozygotic twin studies and 10-20% of 1st-degree relatives of patients meeting criteria for this disorder. Further evidence is seen in studies showing a familial link between somatic symptom disorders and other psychiatric disorders (e.g., higher rates of anxiety and depression in the family members).

Symptom Modeling
Multiple studies have found evidence that a significant proportion of patients with somatic symptom disorders had recently encountered similar symptoms in their local environment or live with family members who complain of similar physical symptoms (e.g., a child with nonepileptic seizures who has a parent or sibling with a seizure disorder).

Parental Responses
Parent beliefs about the significance of symptoms influence the amount of symptoms the child reports. Having a somatic complaint may be more acceptable or noticed in some households than the expression of strong emotions (e.g., anxiety, fear or anger). In such an environment, a child may garner minimal attention for emotional distress, but obtain more attention and sympathy for physical symptoms. Multiple studies have shown that parental protectiveness predicts child functional disability and parental responses (e.g., discouraging activity, expressing concern, and providing comfort) may serve to inadvertently reinforce and maintain illness behaviors.

School and Family Stressors
External environmental factors (e.g., school stress or change in family situation) are common in children presenting with somatic symptom disorders. Common school stressors include bullying, beginning the school year, fear of academic failure, or participation in extracurricular school activities. Dysfunction and less support within the family system are common in somatic symptom disorders. A transition within the family system including death of a family member, birth of a sibling, parental divorce, physical punishment by parents and an increase in the number of arguments between parents have all been linked to somatic symptoms. Nevertheless, there is a significant minority of patients with somatic symptom disorders who do not appear to have obvious psychosocial precipitants for their symptoms. It is unclear whether the absence of recorded stressful events in these patients is because they were unwilling or unable to report relevant stressors or if they were simply absent.

Trauma
Elevated rates of childhood trauma (e.g., childhood sexual, physical, or emotional abuse) have been found in patients with somatic symptom disorders although the trauma prevalence rates in studies vary widely.
Individual
Childhood Physical Illness

There does appear to be a connection between childhood physical illness and the later development of somatization. Many children with somatic symptom disorders have other medical conditions. An antecedent history (e.g., of an accident, viral illness) may trigger onset of symptoms and lead to prolonged recovery or recurrence of symptoms after illness should have subsided. Children who tend to somatize may have a tendency to experience normal somatic sensations as “intense, noxious and disturbing,” referred to as somatosensory amplification. Children with somatic symptom disorders may also have histories of disabling and poorly explained physical symptoms.

Temperament/Coping Styles

Somatic symptoms have been found to be more common in children who are conscientious, sensitive, insecure, internalizers, anxious, and in those who strive for high academic achievement. Somatization may also occur in youngsters who are unable to verbalize emotional distress. Somatic symptoms are often seen as a form of psychological defense against intrapsychic distress that allows the child to avoid confronting anxieties or conflicts, a process referred to as primary gain. “Primary gain” is obtained by keeping the conflict from consciousness and minimizing anxiety. The symptoms may also lead to what is described as “secondary gain” if the symptom results in the child being allowed to avoid unwanted responsibilities or consequences.

Learned Behavior

Somatic complaints may be reinforced (e.g., through a decrease in responsibilities or expectations by others and/or through receiving attention and sympathy as a result of the physical symptoms). Many youngsters may have an antecedent underlying general medical condition that may then be reinforced by parental and/or peer attention as well as additional medical attention in the form of unnecessary tests and investigations.

Psychiatric Comorbidity

There is an association between somatization and other psychiatric illness, in particular depressive and anxiety disorders.

Other Biologic Factors

Research into the pathophysiology of somatic symptom disorders has suggested some unifying mechanisms, including aberrant functions of efferent neural pathways, such as the autonomic nervous system and the hypothalamic–pituitary axis, and alterations in central processing of sensory input. Hyperactivity of the anterior cingulate cortex has been found in patients with conversion disorder, along with impaired activity of the dorsolateral prefrontal cortex. In studies of chronic pain, including migraine and tension type headache, there appears to be progressive loss of gray matter density in brain structures involved in registering pain such as the somatosensory cortex, anterior cingulate cortex and insula. Additionally when there is a strong expectation of pain, the anterior insular cortex is activated in proportion to this expectation.

ASSESSMENT

The majority of patients with somatic symptom and related disorders present in the pediatric rather than mental health settings. It is important for pediatricians to make their diagnosis on the basis of positive symptoms and signs (distressing somatic symptoms plus abnormal thoughts, feelings, and behaviors in response to these symptoms) rather than the absence of a medical explanation. As such, the evaluation of suspected disorders should include an assessment of biologic, psychological, social, and developmental realms both separately and in relation to each other. An integrated approach where both pediatric and mental health clinician are involved in the assessment, management, and treatment is indicated.

Medical

The presence of a physical illness does not exclude the possibility of somatization playing an important role in the child’s presentation. Somatic symptoms early in a disease course that can be directly attributed to a specific physical illness (e.g., acute respiratory illness) may evolve into psychologically based symptoms, particularly in situations in which the child may experience benefit from adopting the sick role. Somatic symptoms may also occur in excess of what would be expected of the symptoms experienced in an existing physical illness. Physical findings may occur secondary to the effects of the somatic symptom disorder, especially when chronic and/or severe (e.g., deconditioning, disuse atrophy and contractures from prolonged immobilization, nutritional deficiency, gastroparesis and constipation from chronic poor oral intake.)

A comprehensive medical work-up to rule out serious physical illness must be carefully balanced with efforts to avoid unnecessary and potentially harmful tests and procedures. The physical examination will find that the child’s symptoms may fluctuate in different contexts, may be anatomically inconsistent or may be in excess of what would be expected from the physical findings.

Psychological

If somatization is suspected, psychiatric consultation should be included early in the diagnostic workup. The reason for consultation should be carefully explained to the family to help avoid the perception that their child’s symptoms are not being taken seriously by the pediatric team (i.e., “it’s in her head”). It should be explained that a complete work-up involves a thorough assessment of the physical and psychological domains of the child and the psychiatric consultation can provide further understanding of the origins of the child’s distress, what perpetuates it and which treatments are likely to be most effective.

The mental health interview should include a careful assessment of the psychological and social stressors and risk factors including a thorough family psychiatric and medical history. The nature of current physical symptoms and any history of prior episodes of somatic symptoms should be included in the assessment, in addition to the child’s emotional, social and academic functioning, coping strategies and family functioning. The evaluation should provide the clinical team with a biopsychosocial explanation of the child’s symptoms, which will inform the treatment plan.

Differential Diagnoses

The primary differential diagnosis is between that of somatic symptom disorder and a physical illness. It is important, however, to be aware that these disorders are not mutually exclusive and often coexist. Mood and anxiety disorders frequently include the presence of physical symptoms which tend to remit with treatment of the primary mood or anxiety disorders and which appear distinct from physical complaints seen in somatic symptom disorders. Chronic pain syndromes may be caused by fibromyalgia and small fiber autonomic neuropathy (see Chapter 168).

MANAGEMENT

With the completion of medical and psychological assessments, a multidisciplinary team meeting of medical and mental health clinicians should be arranged to review all the specialty evaluations and tests, discuss the formulation, diagnostic impressions and treatment recommendations. This should occur to ensure that a consensus has been reached regarding the diagnosis and treatment plan and to facilitate adequate and consistent communication among all providers.

An informing meeting or conference with the family should be facilitated after the above meeting to convey the multidisciplinary team’s diagnostic impressions and treatment recommendations to the patient/family. Medical and mental health clinicians together should communicate the diagnosis (or diagnoses) in a way that families can understand using a comprehensive biopsychosocial formulation. Medical and psychiatric findings should be acknowledged and discussed. Patients and families with somatic symptom disorders often present with the belief that there is primarily a medical cause for their problem and psychosocial contributors are often resisted. Following exhaustive medical investigations which do not yield any unifying
results, labeling the symptoms as “psychiatric” can effectively shift the search for the cause onto family functioning, resulting in youngsters and parents feeling blamed for the symptoms. The team should help the family move towards an understanding of the mind–body connection and shift their approach from searching for the cause of the symptoms to increasing functioning. Providing education about the benefits of treatment and risks of nontreatment is helpful to move the family through the treatment steps.

**Treatment**

An integrated multidisciplinary rehabilitation model is the most suitable for patients with somatic symptom disorders. A rehabilitation model approach provides a useful framework for the treatment that shifts the focus away from finding a cure for symptoms, and instead emphasizes a return to normal adaptive functioning. This includes increased activities of daily living, improved nutrition, enhanced mobility, return to school and socialization with peers.

*Cognitive behavioral interventions* are evidence-based treatments of choice. Cognitive behavioral interventions modify symptom experience including pain perception and restore central nervous system abnormalities that are linked with functional impairment. Components of cognitive behavioral techniques (e.g., relaxation training, biofeedback, and hypnosis) can be used to teach patients the control they can have over certain physiological processes such as autonomic system activity. Cognitive restructuring is effective in addressing and altering dysfunctional thoughts regarding symptoms and their implications for functioning. Treatments that encourage active coping strategies, emotional expression and modulation and limit adolescent reliance on emotional support provided by parents are particularly helpful to more effectively reduce symptoms and improve functioning. Modifying parental response patterns that are overly protective and potentially reinforcing (e.g., allowing the child to sleep late or to stay home from school in response to symptoms) help to decrease disability.

Psychopharmacologic treatment may be considered when other psychiatric disorders are co-occurring, specifically depressive and anxiety disorders. A combination of pharmacotherapy, physical therapy, and psychological interventions in multicomponent management programs has been shown to be effective.

**Treatment Setting**

The majority of patients can be managed in the outpatient setting with appropriate mental health follow-up. Scheduled follow-up visits with the primary care provider (PCP) and other specialists are important to maintain alliance and investment in treatment, prevent doctor shopping, and avoid unnecessary invasive tests and procedures.

Because of the nature of their symptoms, most patients with somatic symptom disorders do not present in mental health settings for their physical complaints and only patients displaying prominent emotional symptoms or who have a concurrent mental disorder are referred to psychiatric services. Medical specialists treat “their own” specialty functional somatic syndrome within their service as a natural consequence of the large number of patients with these disorders presenting at their clinics. The management in these clinics is often multidisciplinary and with primarily medically based treatments and interventions. The existence of various syndrome-specific clinics perpetuates the separate, specialty-dominated approach to somatic symptom disorders and can perpetuate fragmented care rather than moving toward a more integrated model. Although specialized clinics play an important role in the provision of the expertise needed in the evaluation of these patients, they are often not prepared to manage patients who have symptoms involving multiple organ systems. These patients may attend several clinics simultaneously and receive several, parallel, uncoordinated treatments.

A medical home model with mental health clinicians working in collaboration with PCPs and/or different medical specialists may prove to be the most suitable approach for patients with somatic symptom disorders. Collocated medical and mental health services improve communication, decrease fragmentation of services, and decrease the stigma and resistance some families may have with attending psychiatric clinics. The efficacy of a treatment program with comprehensive multidisciplinary services and cognitive behavioral treatment has been studied in a randomized, controlled trial, and the results showed immediate, clinically relevant benefits that were sustained at the 1-year follow-up.

Patients with profound and pervasive functional impairment likely will need more intensive psychiatric treatment (e.g., a medical-psychiatric partial hospital program or inpatient unit). Multidisciplinary inpatient rehabilitation programs have a great deal to offer these patients as they are designed to support both physical and psychological recovery. Families feel reassured that multidisciplinary staff can continue to monitor symptoms, thus ensuring that any missed diagnoses will be recognized quickly.

Children with a high level of impairment often miss a significant amount of school; communication with the school in such cases is often crucial in helping a successful transition back and improving overall functioning. In addition to discussions with the school guidance counselor and nurse, a letter for the school providing education and recommended approaches for patient’s symptoms is often beneficial. Ongoing communication between the school and PCP for monitoring of further symptoms is recommended.

*Bibliography is available at Expert Consult.*
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Rumination disorder is the repeated regurgitation of food, where the regurgitated food may be rechewed, reswallowed, or spit out, for a period of at least 1 mo following a period of normal functioning. Regurgitation is typically frequent and daily; it does not occur during sleep. It is not caused by an associated gastrointestinal illness or other medical condition (e.g., gastroesophageal reflux or pyloric stenosis). It does not occur exclusively during the course of anorexia nervosa, bulimia nervosa, binge-eating disorder, or avoidant/restrictive food intake disorder. If the symptoms occur in the context of an intellectual developmental disorder or another neurodevelopmental disorder, they must be sufficiently severe to warrant additional clinical attention.

Weight loss and failure to make expected weight are common features in infants with rumination disorder. Infants may display a characteristic position of straining and arching the back with the head held back, making sucking movements with their tongue. In infants and older individuals with intellectual disability, the rumination behavior may appear to have a self-soothing or self-stimulating function. Malnutrition may occur in older children and adults, particularly when the regurgitation is associated with restricted food intake (which may be designed to avoid regurgitation in front of others). They may attempt to hide the regurgitation behavior or avoid eating among others.

**EPIDEMIOLOGY**

Originally thought of as a disorder predominantly seen in infants and those with intellectual disability, rumination disorder has also been recognized in healthy individuals across the life span. Prevalence data
for rumination disorder are inconclusive. In otherwise healthy children, this disorder typically appears in the first year of life, generally between the ages of 3 and 12 mo. The disorder can have an episodic course or occur continuously until treatment is initiated. In infants, the disorder frequently remits spontaneously, but can be protracted with problematic and even life-threatening malnutrition. Additional complications related to the secondary effects of malnutrition included growth delay and negative effect on development and learning potential.

**ETIOLOGY AND DIFFERENTIAL DIAGNOSIS**

Risk factors for rumination disorder in infants and young children include a disturbed relationship with primary caregivers, lack of an appropriately stimulating environment, neglect, stressful life situations, learned behavior reinforced by pleasurable sensations, distraction from negative emotions, and/or inadvertent reinforcement (attention) from primary caregivers. The differential diagnosis includes congenital gastrointestinal system anomalies, pyloric stenosis (see Chapter 329), Sandifer syndrome (see Chapter 323), gastroparesis, hiatal hernia (see Chapter 322), increased intracranial pressure, diencephalic tumors, adrenal insufficiency, and inborn errors of metabolism. Older children and adults with anorexia nervosa or bulimia nervosa may also engage in regurgitation because of concerns about weight gain. The diagnosis of rumination disorder is appropriate only when the severity of the disturbance exceeds that routinely associated with a concurrent physical illness or mental disorder.

**TREATMENT**

This first step in treatment begins with a behavioral analysis to determine if the disorder serves as a self-stimulation purpose and/or is socially motivated. The behavior may begin as self-stimulation, but it subsequently becomes reinforced and maintained by the social attention given to the behavior. The central focus of behavioral treatment is to reinforce correct eating behavior while minimizing attention to rumination. Diaphragmatic breathing and postprandial gum chewing when used as a competing response have been shown to be helpful. Aversive conditioning techniques (e.g., withdrawal of positive attention) are considered when a child's health is jeopardized.

Successful behavioral treatment requires the child's primary caregivers to be involved in the intervention. The caretakers need education and counseling around responding adaptively to the child's behavior as well as altering any maladaptive responses. There is no current evidence supporting a psychopharmacologic intervention for this disorder. In more severe or intractable cases (e.g., severe dehydration and malnutrition), an intensive integrated medical-behavioral treatment program afforded on a medical or medical-psychiatric unit may be necessary.

Bibliography is available at Expert Consult.

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**23.2 Pica**

*Emily R. Katz, Robert L. Kitts, and David R. DeMaso*

Pica involves the persistent eating of nonnutritive, nonfood substances (e.g., paper, soap, plaster, charcoal, clay, wool, ashes, paint, earth) over a period of at least 1 mo. The eating behavior is inappropriate to the developmental level (e.g., the normal mouthing and tasting of objects in infants and toddlers) and, therefore, a minimum age of 2 yr is suggested. The eating behavior is not part of a culturally supported or socially normative practice. A diagnosis of pica may be assigned in the presence of any other feeding and eating disorder.

**EPIDEMIOLOGY**

Pica can occur throughout the lifetime, but occurs most commonly in childhood. It appears to be more common in those with intellectual disability and autism spectrum disorders, and to a lesser degree in obsessive-compulsive and schizophrenic disorders. The prevalence of pica is unclear, although it appears to increase with the severity of an intellectual disability. It usually remits in childhood but can continue into adolescence and adulthood. *Geophagia* (eating earth) is associated with pregnancy and is not seen as abnormal in some cultures (e.g., rural or preindustrial societies in parts of Africa and India). Children with pica are at increased risk for lead poisoning (see Chapter 721), iron-deficiency anemia (see Chapter 455), mechanical bowel problems, intestinal obstruction, intestinal perforations, dental injury, and parasitic infections. It can be fatal based on substances ingested.

**ETIOLOGY AND DIFFERENTIAL DIAGNOSIS**

Numerous etiologies have been proposed but not proved, ranging from psychosocial causes to physical ones. They include nutritional deficiencies (e.g., iron, zinc, and calcium), low socioeconomic factors (e.g., lead paint exposure), child abuse and neglect, family disorganization (e.g., poor supervision), mental disorder, learned behavior, underlying (but undetermined) biochemical disorder, and cultural and familial factors. The differential diagnosis includes anorexia nervosa (see Chapter 28), factitious disorder, and nonsuicidal self-injury in personality disorders. A separate diagnosis of pica should be made only if the eating behavior is sufficiently severe enough to warrant additional clinical attention.

**TREATMENT**

Combined behavioral, social, and medical approaches are generally indicated for pica. Assessment for neglect and family supervision combined with a psychiatric assessment for cooccurring mental disorders and developmental delay are important in developing an effective intervention strategy for pica. Behavioral treatment interventions, particularly applied behavioral analysis in patients with intellectual disability or autism spectrum disorders, have increasing evidence for being helpful. The sequelae related to an ingested item can require specific treatment (e.g., lead toxicity, iron-deficiency anemia, parasitic infestation). Ingestion of hair can require medical or surgical intervention for a gastric bezoar (see Chapter 334.2).

Bibliography is available at Expert Consult.

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**23.3 Enuresis (Bed-Wetting)**

See Chapter 543.

**23.4 Encopresis**

See Chapter 332.2.
Bibliography

Bibliography
Motor disorders are interrelated sets of psychiatric symptoms characterized by abnormal motor movements and associated phenomena. In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), motor disorders include tic, stereotypic movement, and developmental coordination disorders. Tic disorders (Tourette, persistent motor or vocal tic, provisional tic) and stereotypic movement
disorder will be addressed in this chapter. Although not DSM-5 motor disorders, habits present as repetitive and often problematic motor behaviors (specifically thumb sucking and teeth grinding).

### 24.1 Tic Disorders

*Colleen A. Ryan, Michael L. Trieu, David R. DeMaso, and Heather J. Walter*

**Tourette disorder (TD), persistent (chronic) motor or vocal tic (PTD),** and provisional tic disorders (Table 24-1) are characterized by involuntary, rapid, repetitive, single or multiple motor and/or vocal/phonic tics that wax and wane in frequency but have persisted for more than 1 year since first tic onset (<1 year for provisional tic disorder). PTD is differentiated from TD in that TD is limited to either motor or vocal tics (not both), whereas TD has both motor and vocal tics at some point in the illness (although not necessarily concurrently). The tic disorders are hierarchical in order (i.e., TD followed by PTD followed by provisional tic disorder), such that once a tic disorder at one level of the hierarchy is diagnosed, a lower hierarchy diagnosis cannot be made.

#### DESCRIPTION

Tics are sudden, rapid, recurrent, nonrhythmic motor movements or vocalizations. Simple motor tics (e.g., eye blinking, neck jerking, shoulder shrugging, extension of the extremities) are fast, brief movements involving one or a few muscle groups, while complex motor tics involve sequentially and/or simultaneously produced relatively coordinated movements that can seem purposeful (e.g., brushing back one’s hair bangs, tapping the foot, imitating someone else’s movement [echo-praxia], or making a sexual or obscene gesture [copropraxia]). Simple vocal tics (e.g., throat clearing, sniffing, coughing) are solitary, meaningless sounds and noises, whereas complex vocal tics (e.g., partial words [syllables], words out of context, coprolalia [obscenities or slurs], palilalia [repeating one’s own sounds or words], or echolalia [repeating the last heard word or phrase]) are meaningful utterances and verbalizations.

Sensory phenomena (premonitory urges) that precede and trigger the urge to tic have been described. Individuals with tics can suppress them for varying periods of time, particularly when external demands exert their influence, when deeply engaged in a focused task or activity, or during sleep. Tics are often suggestible and are worsened by anxiety, excitement, or exhaustion. Although parents have described increasing frequency of tics at the end of the day, research has not supported volitional suppressing of tics leading to tic rebound.

#### CLINICAL COURSE

Onset of tics is typically between ages 4 and 6 yr. Peak severity occurs between ages 10 and 12 yr, with marked attenuation of tic severity in most individuals (65%) by age 18–20 yr. A small percentage will have worsening tics into adulthood. New onset of tics in adulthood is very rare and most often is associated with exposure to drugs or insults to the central nervous system. Tics manifest similarly in all age groups and change in affected muscle groups and vocalizations over time. Some individuals may have tic-free periods of weeks to months.

#### EPIDEMIOLOGY

Prevalence rates for all tics range from 6-18% for boys and 3-11% for girls, with the rate of TD alone estimated as 0.3-0.8%. In general, PTD/TD has a male preponderance with a gender ratio varying from 2:1 to 4:1. Evidence supports higher rates in white compared to African-American or Hispanic youth.

#### DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes the repetitive movements of childhood (Table 24-2). Tics may be difficult to differentiate from stereotypies. Although stereotypies may resemble tics, stereotypies are typically rhythmic movements and do not demonstrate the change in body location or movement type over time that is typical of tics. Compulsions may be difficult to differentiate from tics when tics have premonitory urges. Tics should be differentiated from a variety of developmental and benign movement disorders (e.g., benign paroxysmal torticollis, Sandifer syndrome, benign jitteriness of newborns, and shuddering attacks). Tics may present in various neurologic illnesses (e.g., Wilson disease, neuroacanthocytosis, Huntington syndrome, and a variety of frontal-subcortical brain lesions); it is rare for tics to be the only manifestation of these disorders. Individuals presenting with tics in the context of declining motor or cognitive function should be referred for neurologic assessment. Some substances/medications that are reported to worsen tics include stimulants, selective serotonin reuptake inhibitors, lamotrigine, and cocaine. If tics develop in close temporal relationship to the use of a substance/medication and then remit when use of the substance is discontinued, a causal relationship is possible. Although a long-time clinical concern, there is no scientific evidence in controlled studies that stimulants increase tics.

#### COMORBIDITIES

Co-occurring psychiatric disorders are common, often with both the patient and family viewing the accompanying condition as more problematic than the tics per se. There is a bidirectional association between PTD/TD (especially TD) and obsessive-compulsive disorder (OCD; see Chapter 25), with 20-40% of TD patients meeting OCD criteria and 20-40% of OCD patients reporting tics (Fig. 24-1). Attention-deficit/hyperactivity disorder (ADHD; see Chapter 33) co-occurs in approximately 50% of all childhood PTD/TD, but estimates

### Table 24-1 DSM-5 Diagnostic Criteria for Tic Disorders

| Note: A tic is a sudden, rapid, recurrent, nonrhythmic motor movement or vocalization. |
| TOURETTE’S DISORDER |
| A. Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently. |
| B. The tics may wax and wane in frequency but have persisted for more than 1 year since first tic onset. |
| C. Onset is before age 18 years. |
| D. The disturbance is not attributable to the physiological effects of a substance (e.g., cocaine) or another medical condition (e.g., Huntington’s disease, postural encephalitis). |

| PERSISTENT (CHRONIC) MOTOR OR VOCAL TIC DISORDER |
| A. Single or multiple motor or vocal tics have been present during the illness, but not both motor and vocal. |
| B. The tics may wax and wane in frequency but have persisted for more than 1 year since first tic onset. |
| C. Onset is before age 18 years. |
| D. The disturbance is not attributable to the physiological effects of a substance (e.g., cocaine) or another medical condition (e.g., Huntington’s disease, postural encephalitis). |
| E. Criteria have never been met for Tourette’s disorder. |
| Specify if: |
| With motor tics only |
| With vocal tics only |

| PROVISIONAL TIC DISORDER |
| A. Single or multiple motor and/or vocal tics. |
| B. The tics have been present for less than 1 year since first tic onset. |
| C. Onset is before age 18 years. |
| D. The disturbance is not attributable to the physiological effects of a substance (e.g., cocaine) or another medical condition (e.g., Huntington’s disease, postural encephalitis). |
| E. Criteria have never been met for Tourette’s disorder or persistent (chronic) motor or vocal tic disorder. |

From the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013), American Psychiatric Association, p. 81.
in clinically referred patients suggest much higher rates (60–80%). PTD/TD is often accompanied by behavior problems including poor frustration tolerance, temper outbursts, and oppositionality. Learning disabilities have been found in more than 20% of these patients. The co-occurrence of anxiety and depression also has been observed. Some

patients with PTD/TD will display symptoms of autism spectrum disorders (ASDs; see Chapter 30); careful assessment is required to determine which disorder is primary.

ETIOLOGY

Tics are proposed to be the result of dysfunctional corticostriatal–thalamocortical motor pathways in the basal ganglia, striatum, and frontal lobes associated with abnormalities in the dopamine, serotonin and norepinephrine neurotransmitter systems. Male predominance in PTD/TD may be attributable to influences of sex hormones on the neurodevelopment of these motor pathways, as reflected by the effects of antiandrogens in the treatment of TD.

Family studies suggest a 10–100–fold increase in the risk of PTD/TD among 1st-degree relatives compared to rates in the general population. Twin studies also support a genetic link, with approximately 80% of monozygotic twins and 30% of dizygotic twins showing concordance for PTD/TD. To date, candidate-gene association and nonparametric linkage studies have not shown specific susceptibility genes for PTD/TD.

Autoimmune mediated mechanisms have been hypothesized as having a potential etiologic role in some tic disorders. The pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS; see Chapter 183) designation has been used to describe cases of acute childhood onset of OCD and/or tics following a streptococcal infection. More recently, PANS (pediatric acute-onset neuropsychiatric syndrome) has been used to describe a subtype of acute childhood onset OCD (tics are not a required feature) in which a link to a prior streptococcal infection is not evident suggesting that other infectious agents may also be responsible (Table 24-3). In addition to a diagnosis of OCD and/or tics, children with PANS/PANDAS have been reported to have symptoms of separation anxiety, nightmares, personality change, oppositional behaviors, and deterioration in math skills and handwriting. Although some studies suggest a prior history of infections may increase the risk for developing tic disorder, this remains controversial.

Premorbid stress has been hypothesized to act as a sensitizing agent in the pathogenesis of TD among susceptible individuals by affecting

![Figure 24-1 Schematic representation of the behavioral spectrum in Tourette syndrome. The size of each area is proportional to the estimated prevalence of the symptoms; the background color intensity is proportional to the complexity of the clinical presentation. From Cavanna AE, Seri S: Tourette’s syndrome. BMJ 347:f4964, 2013.](image-url)
stress responsive biologic systems such as the hypothalamic–pituitary–adrenal axis.

**SEQUELAE**

Many individuals with mild to moderate tics express little to no distress or functional impairment and may even be unaware of their tics. Even individuals with moderate to severe tics can experience little functional impairment, but psychological distress may occur. Uncommonly, the presence of tics can lead to social isolation, social victimization, inability to work or attend school, or impaired quality of life.

**SCREENING**

Pediatricians should routinely screen for unusual movements and vocalizations. As an adjunct to a verbal screen, commonly used broad-band symptom rating scales such as the Child Behavior Checklist (CBCL) and the Swanson, Nolan, and Pelham (SNAP) include specific tic questions. Often families are unaware that frequent sniffing, coughing, or blinking may be indicative of tics, attributing these behaviors to medical problems (e.g., allergies, visual problems). A careful assessment of the timing, triggers, and specific characteristics may differentiate tics from other medical problems. If differentiation is difficult, a referral to a pediatric specialist in the affected system is warranted.

**ASSESSMENT**

If the screening suggests the presence of a tic disorder, a more comprehensive evaluation should ensue, including the age of onset, types of tics, tic frequency, alleviating and aggravating factors, and a family history of tics. Symptom rating scales specific for tics (e.g., the Motor tic, Obsessions and compulsions, Vocal tic Evaluation Survey [MOVES], Tic Self Report Scale, Tourette’s Disorder Scale, Parent Tic Questionnaire [PTQ]; http://www.uab.edu/ot/practice/tourette-syndrome-clinic/parent-tic-questionnaire), and the Child Tourette’s Disorder Impairment Scale–Parent Version can supplement the assessment. For clinician-rated tic severity, the most commonly used instrument is the Yale Global Tic Severity Scale (YGTTSS); the Tourette Syndrome Severity Scale (TSSS), and the Tourette Syndrome Global Scale (TSGS) also can be useful.

A medical workup should be considered for new-onset tics, particularly for presentations characterized by sudden onset, atypicity, or mental status abnormalities. Basic laboratory measures (hemogram, renal/hepatic function panel, thyroid panel and ferritin along with urine drug screen for adolescents) should be considered. For new sudden (overnight) onset or severe symptom exacerbation, pediatricians may assess for co-occurring acute infection (e.g., culture, rapid viral tests, etc.). Electroencephalogram and brain imaging are not routinely recommended and should be reserved for cases with other neurologic findings that might suggest an autoimmune encephalitis syndrome (limbic encephalitis) (see Chapter 598.4). Cooccurring psychiatric disorders (e.g., OCD, ADHD, ASD) should be investigated.

**TREATMENT**

The decision to treat tics is made with the child and family based upon the level of impairment and distress caused by the tics. If tics are mild in severity, there may be no need for intervention after psychoeducation is provided.

Psychoeducation should include common symptom presentations, implications of co-occurring conditions, course and prognosis, and treatment options (including no treatment). The youth’s typical exacerbating and alleviating factors should be reviewed. The clinician can direct the family and youth to informational websites, including the Tourette Syndrome Association (www.tsa-usa.org) or the Tourette Syndrome “Plus” website (www.tourettesyndrome.net).

Nearly 75% of children with TD/PDT receive some form of classroom accommodation (most often ignoring the tics and permission to leave the room as needed). The accommodations may need to be formalized in an Individualized Education Plan (IEP) or 504 Plan.

Referral to a behavioral treatment specialist should be considered when tics are distressing or functionally impairing. The behavioral intervention with the strongest empirical support is habit reversal therapy (HRT). The typical components of HRT include premonitory urge awareness training, building a competing response to the urge to tic, and social support. In a large randomized trial comparing an HRT protocol to a psychosocial control, the effect size favoring the intervention was 0.64; nearly all intervention subjects were also prescribed medication. To date, there are no studies comparing HRT to medication or combined (medication plus HRT) therapy.

Behavioral treatment may also address less-adaptive coping strategies (e.g., avoidance, social withdrawal) that develop secondary to tics and contribute to impairment. Skill-based therapies such as cognitive-behavioral therapy can be beneficial in reducing maladaptive coping strategies, anxiety, and compulsive behavior.

Medications should be considered when the tics are causing severe impairment in the quality of life, or when medication-responsive psychiatric comorbidities are present that target both tic symptoms and comorbid conditions. The only 2 FDA-approved medications to treat TD are haloperidol and pimozide, although most clinicians use atypical antipsychotics (risperidone) before the FDA-approved agents because of the more favorable side-effect profile of the atypicals. Others use α₂-agonists as 1st-line agents because of their less-adverse side-effect profile compared to the antipsychotics.

The α₂-adrenergic agonists (clonidine and guanfacine) have demonstrated an effect size of 0.5 for amelioration of tics. A meta-analysis found that agonist trials enrolling subjects with comorbid ADHD demonstrated a much higher effect size (0.68) than trials enrolling subjects without comorbid ADHD (0.15). The starting dose for clonidine is 0.025-0.05 mg/day with gradual increases up to 0.1-0.4 mg/day, administered in divided doses (3-4 times a day). A transdermal patch of clonidine is available, as is a sustained-release formulation that has been FDA-approved for the treatment of ADHD, but has not been studied for the treatment of tics. Sedation and low blood pressure are

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### Table 24-3: Diagnostic Criteria Proposed for Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS)

<table>
<thead>
<tr>
<th>CRITERION</th>
<th>DESCRIPTION</th>
</tr>
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<tbody>
<tr>
<td>I. Abrupt, dramatic onset of obsessive-compulsive disorder or severely restricted food intake</td>
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<tr>
<td>II. Concurrent presence of additional neuropsychiatric symptoms, with similarly severe and acute onset, from at least 2 of the following 7 categories (see text for full description):</td>
<td></td>
</tr>
<tr>
<td>1. Anxiety</td>
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<tr>
<td>2. Emotional lability and/or depression</td>
<td></td>
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<tr>
<td>3. Irritability, aggression and/or severely oppositional behaviors</td>
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<tr>
<td>4. Behavioral (developmental) regression</td>
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</tr>
<tr>
<td>5. Deterioration in school performance</td>
<td></td>
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<tr>
<td>6. Sensory or motor abnormalities</td>
<td></td>
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<tr>
<td>7. Somatic signs and symptoms, including sleep disturbances, enuresis or urinary frequency</td>
<td></td>
</tr>
<tr>
<td>III. Symptoms are not better explained by a known neurologic or medical disorder, such as Sydenham chorea, systemic lupus erythematosus, Tourette disorder or others. Note: The diagnostic work-up of patients suspected of PANS must be comprehensive enough to rule out these and other relevant disorders. The nature of the co-occurring symptoms will dictate the necessary assessments, which may include MRI scan, lumbar puncture, electroencephalogram or other diagnostic tests.</td>
<td></td>
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</tbody>
</table>

common side effects that require careful monitoring, particularly when initiating treatment. The role of guanfacine, which is a less-sedating \( \alpha_2 \)-agonist, has not been firmly established but trials are underway.

The \( D_2 \) dopamine receptor-blocking medications (haloperidol and pimozide) are effective in reducing tics, but the side-effect burden (e.g., extrapyramidal symptoms) have limited their use as 1st-line treatment. Risperidone, an atypical antipsychotic medication, has appeared in 4 randomized control trials to be an effective treatment, although concerns for neuromotor and metabolic side effects exist. The starting dose for risperidone is 0.125-0.5 mg/day with a usual dose range of 0.75-3.0 mg/day.

The side effects of all antipsychotic medications warrant close monitoring; abnormal movements should be monitored periodically using a standardized methodology (such as the Abnormal Involuntary Movement Scale [AIMS] checklist); blood pressure, body mass index and fasting glucose and lipids should be checked at baseline and at regular intervals thereafter, according to standard guidelines. Consideration of weight management interventions and increased monitoring of blood glucose and lipid levels should be implemented if weight gain exceeds 90th percentile body mass index for age, or a change of 5 body mass index units occurs in youths who were obese at the beginning of treatment. In patients with a personal or family history of cardiac abnormalities, including syncope, palpitations, arrhythmias, or sudden unexplained death, a baseline electrocardiogram with subsequent monitoring should be considered, along with cardiology consultation. Alternative pharmacology should be considered if the resting heart rate exceeds 130 beats/min, or the PR, QRS, and QTc exceed 200, 120, and 460 msec, respectively.

Children with tic disorders may benefit from selective serotonin reuptake inhibitors (SSRIs) for the treatment of comorbid OCD, anxiety, or depressive disorders. Augmentation of SSRIs with an atypical antipsychotic medication has been a consideration in patients with co-occurring tic disorders and OCD responding poorly to an SSRI alone. The presence of tics does not preclude the use of stimulants to address comorbid ADHD. However, close clinical monitoring is required for possible exacerbation of tics during stimulant treatment. Anger and rage outbursts are not uncommon among youth with tics (up to 80% in clinically referred samples). Behavioral therapies that address anger management may be useful. There are no controlled pharmacologic studies in youth with tics disorders with anger outbursts. There also is no scientific evidence to support the use of deep brain stimulation, repetitive magnetic stimulation, and dietary supplements in the treatment of TD/PTD.

### 24.2 Stereotypic Movement Disorder

Colleen A. Ryan, Michael L. Trieu, David R. DeMaso, and Heather J. Walter

In DSM-5, stereotypic movement disorder (SMD) is defined as a neurodevelopmental disorder characterized by repetitive, seemingly driven, and apparently purposeless motor behavior (stereotypy) that interferes with social, academic, or other activities that may result in self-injury. The onset of SMD is the early developmental period (often before age 3 yr), and the symptoms are not attributable to the physiologic effects of a substance or neurologic condition and are not better explained by another neurodevelopmental or mental disorder. The disorder is considered mild if symptoms are easily suppressed by sensory stimulus or distraction, and severe if continuous monitoring and protective measures are required to prevent serious injury, with moderate falling between mild and severe.

#### DESCRIPTION

Examples of stereotypic movements include hand shaking or waving, body rocking, head banging, self-biting, and hitting one’s own body. The presentation depends on the nature of the stereotypic movement and level of the child’s awareness of the behavior. Among typically developing children, the repetitive movements may be stopped when attention is directed to them or when the child is distracted from performing them. Among children with neurodevelopmental disorders, the behaviors are typically less responsive to such efforts. Each individual presents with his or her own uniquely patterned behavior. Stereotypic movements may occur many times during a day, lasting a few seconds to several minutes or longer. The behaviors may occur in multiple contexts, including when the individual is excited, stressed, fatigued, or bored.

#### CLINICAL COURSE

Stereotypic movements typically begin within the first 3 yr of life. In children who develop complex motor stereotypies, the great majority exhibit symptoms before 24 mo of age. In most typically developing children, these movements resolve over time. Among individuals with intellectual disability, the stereotyped behaviors may persist for years, although the pattern may change over time.

#### EPIDEMIOLOGY

Simple stereotypic movements (e.g., rocking) are common in typically developing young children. Self-injurious habits, such as self-biting or head banging, can occur in up to 25% of typically developing toddlers, but they are almost invariably associated with developmental delay in children older than age 5 yr. Complex stereotypic movements are much less common (occurring in approximately 3-4% of children). Between 4% and 16% of individuals with intellectual disability engage in stereotypic movements.

#### COMORBIDITY

Stereotypic movements are a common manifestation of a variety of neurogenetic disorders, such as Lesch-Nyhan syndrome, Rett syndrome (see Chapter 599), fragile X syndrome (see Chapter 81), Cornelia de Lange syndrome, and Smith-Magenis syndrome.

#### DIFFERENTIAL DIAGNOSIS

According to DSM-5, stereotypic movements must be differentiated from normal development, ASDs, tic disorders, OCDs, and other neurologic and medical conditions. Simple stereotypic movements occurring in the context of normal development usually resolve with age. Stereotypic movements may be a presenting symptom of ASD, but SMD does not include the deficits in social communication characteristic of ASD. When ASD is present, SMD is diagnosed only when there is self-injury or when the stereotyped behaviors are sufficiently severe to become a focus of treatment. Typically, SMD has an earlier age of onset than the tic disorders, and the movements are fixed in their pattern. SMD is distinguished from OCD by the absence of obsessions as well as the nature of the repetitive behaviors, which in OCD are purposeful (e.g., in response to obsessions). The diagnosis of stereotypic movements requires the exclusion of habits, mannerisms, paroxysmal dyskinesias, and benign hereditary chorea. A neurologic history and examination are required to assess features suggestive of other disorders, such as myoclonus, dystonia, and chorea.

#### ETIOLOGY

There is a possible evolutionary link between repetitive abnormal grooming-like behaviors and early human experience with adversity. Brain regions implicated in this model (e.g., amygdala and hippocampus) are those involved in navigating human experience through unpredictable, anxiety-provoked emotional states as well as regions (e.g., nucleus accumbens) related to pleasure and reward seeking. The latter involves the hypothesis that individuals experience some level of gratification from performing the habit behavior. Social isolation with insufficient stimulation (e.g., severe neglect; see Chapter 40) is a risk factor for self-stimulation that may progress into stereotypies (particularly repetitive rocking or spinning). Environmental stress may trigger stereotypic behaviors. Repetitive self-injurious behavior may be a behavioral phenotype in neurogenetic syndromes (e.g., Lesch-Nyhan, Rett, and Cornelia de Lange syndromes). Lower cognitive functioning is also linked to greater risk of stereotypic behaviors.
Thumb Sucking
Thumb sucking is common in infancy and in as many as 25% of children age 2 yr and 15% of children age 5 yr. Thumb sucking beyond 5 yr may be associated with sequelae (paronychia, anterior open bite). Like other rhythmic patterns of behavior, thumb sucking is self-soothing. Basic behavioral management, including encouraging parents to ignore thumb sucking and instead focus on praising the child for substitute behaviors, is often effective treatment. Simple reminders and reinforcers, such as giving the child a sticker (or other rewards) for each block of time that he or she does not suck the thumb can also be considered. Although some suggest the use of noxious agents (bitter salves) this approach should rarely be necessary.

Bruxism
Bruxism or teeth grinding is common (5-30% of children), can begin in the first 5 yr of life, and may be associated with daytime anxiety. Persistent bruxism can manifest as muscular or temporomandibular joint pain. Untreated bruxism can cause problems with dental occlusion. Helping the child find ways to reduce anxiety might relieve the problem; bedtime can be made more relaxing by reading or talking with the child and allowing the child to discuss fears. Praise and other emotional support are useful. Persistent bruxism requires referral to a dentist given the risk for dental occlusion.

Bibliography is available at Expert Consult.
Chapter 24 ♦ Motor Disorders and Habits 144.e1

Bibliography


Anxiety, defined as dread or apprehension is not considered pathologic, is seen across the life span, and can be adaptive (e.g., the anxiety one might feel during an automobile crash). Anxiety has both a cognitive and behavioral component, expressed in worrying and wariness, and a physiologic component, mediated by the autonomic nervous system. Anxiety disorders are characterized by pathologic anxiety in which anxiety becomes disabling, interfering with social interactions, development, and achievement of goals or quality of life, and can lead to low self-esteem, social withdrawal, and academic underachievement. The average age of onset of anxiety disorder is 11 yr. Diagnosis of a particular anxiety disorder in a child requires significant interference in the child’s psychosocial and/or academic or occupational functioning, which can occur even with subthreshold symptoms that do not meet criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Anxiety may have physical manifestations such as weight loss, pallor, tachycardia, tremors, muscle cramps, paresthesias, hyperhidrosis, flushing, hyperreflexia, and abdominal tenderness.

Separation anxiety disorder (SAD), childhood-onset social phobia or social anxiety disorder, generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), phobias, posttraumatic stress disorder (PTSD), and panic disorder (PD) are all defined by the occurrence of either diffuse or specific anxiety, often related to predictable situations or cues. Anxiety disorders are the most common psychiatric disorders of childhood; they occur in 5-18% of all children and adolescents, prevalence rates comparable to physical disorders such as asthma and diabetes. Anxiety disorders are often comorbid with other psychiatric and medical disorders (including a second anxiety disorder); significant impairment in day-to-day functioning is common. High levels of fear in adolescence are also a significant risk factor for experiencing later episodes of major depression in adulthood. Anxiety
Anxiety and depressive disorder in adolescence predict increased risk of anxiety and depressive symptoms (including suicide attempts) in adulthood, underscoring the need to diagnose and treat these underreported, yet prevalent, conditions early. 

Because anxiety is both a normal phenomenon and, when highly activated, strongly associated with impairment, the pediatrician must be able to differentiate normal anxiety from abnormal anxiety across development. Anxiety has an identifiable developmental progression for most children; most infants exhibit stranger wariness or anxiety beginning at 7-9 mo of age. Behavioral inhibition to the unfamiliar (withdrawal or fearfulness to novel stimuli associated with physiologic arousal) is evident in approximately 10-15% of the population at 12 mo of age and is moderately stable. Most children who show behavioral inhibition do not develop impairing levels of anxiety. A family history of anxiety disorders and maternal over involvement or enmeshment predicts later clinically significant anxiety in behaviorally inhibited infants. The infant who is excessively clingy and difficult to calm during pediatric visits should be followed for signs of increasing levels of anxiety.

Preschoolers typically have specific fears related to the dark, animals, and imaginary situations, in addition to normative separation anxiety. Preoccupation with orderliness and routines (just right phenomena) often takes on a quality of anxiety for preschool children. Parents’ reassurance is usually sufficient to help the child through this period. Although most school-age children abandon the imaginary fears of early childhood, some replace them with fears of bodily harm or other worries (Table 25-1). In adolescence, general worrying about school performance and worrying about social competence are common and remit as the teen matures.

<table>
<thead>
<tr>
<th>Table 25-1</th>
<th>DSM-5 Diagnostic Criteria for Specific Phobia</th>
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<tbody>
<tr>
<td><strong>Diagnostic Criteria</strong></td>
<td></td>
</tr>
<tr>
<td>A. Marked fear or anxiety about a specific object or situation (e.g., flying, heights, animals, receiving an injection, seeing blood).</td>
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<tr>
<td><strong>Note:</strong> In children, the fear or anxiety may be expressed by crying, tantrums, freezing, or clinging.</td>
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</tr>
<tr>
<td>B. The phobic object or situation almost always provokes immediate fear or anxiety.</td>
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<tr>
<td>C. The phobic object or situation is actively avoided or endured with intense fear or anxiety.</td>
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<tr>
<td>D. The fear or anxiety is out of proportion to the actual danger posed by the specific object or situation and to the sociocultural context.</td>
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<tr>
<td>E. The fear, anxiety, or avoidance is persistent, typically lasting for 6 mo or more.</td>
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<tr>
<td>F. The fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.</td>
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<tr>
<td>G. The disturbance is not better explained by the symptoms of another mental disorder, including fear, anxiety and avoidance or situations associated with panic-like symptoms or other incapacitating symptoms (as in agoraphobia); objects or situations related to obsessions (as in obsessive-compulsive disorder); remnants of traumatic events (as in posttraumatic stress disorder); separation from home or attachment figures (as in separation anxiety disorder); or social situations (as in social anxiety disorder).</td>
<td></td>
</tr>
<tr>
<td><strong>Specify if:</strong></td>
<td></td>
</tr>
<tr>
<td>Code based on the phobic stimulus:</td>
<td></td>
</tr>
<tr>
<td>Animal (e.g., spiders, insects, dogs).</td>
<td></td>
</tr>
<tr>
<td>Natural environment (e.g., heights, storms, water).</td>
<td></td>
</tr>
<tr>
<td>Blood-injection-injury (e.g., needles, invasive medical procedures).</td>
<td></td>
</tr>
<tr>
<td>Situational (e.g., airplanes, elevators, enclosed places).</td>
<td></td>
</tr>
<tr>
<td>Other (e.g., situations that may lead to choking or vomiting; in children, e.g., loud sounds or costumed characters).</td>
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</tbody>
</table>

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013) American Psychiatric Association, pp. 197-198.

Genetic or temperamental factors contribute more to the development of some anxiety disorders, whereas environmental factors are closely linked to the cause of others. Specifically, behavioral inhibition appears to be a heritable tendency and is linked with social phobia, generalized anxiety, and selective mutism, OCD and other disorders associated with OCD-like behaviors, such as Tourette syndrome and other tic disorders, tend to have high genetic risk as well (see Chapter 24.1). Environmental factors, such as parent–infant attachment and exposure to trauma, contribute more to SAD and PTSD. Parental anxiety disorder is associated with an increased risk of anxiety disorder in offspring. Differences in the size of the amygdala and hippocampus are noted in patients with anxiety symptoms.

**SAD** is one of the most common childhood anxiety disorders with a prevalence of 3.5-5.4%. Approximately 30% of children presenting to an outpatient anxiety disorder clinic have SAD as a primary diagnosis. Separation anxiety is developmentally normal when it begins about 10 mo of age and tapers off by 18 mo. By 3 yr of age, most children can accept the temporary absence of their mother or primary caregiver.

SAD is more common in prepubertal children, with an average age of onset of 7.5 yr. Girls are more commonly affected than boys. SAD is characterized by unrealistic and persistent worries about separation from the home or a major attachment figure. Concerns include possible harm befalling the affected child or the child’s primary caregivers, reluctance to go to school or to sleep without being near the parents, persistent avoidance of being alone, nightmares involving themes of separation, numerous somatic symptoms, and complaints of subjective distress. The first clinical sign might not appear until 3rd or 4th grade, typically after a holiday or a period where the child has been home because of illness, or when the stability of the family structure has been threatened by illness, divorce, or other psychosocial stressor.

Symptoms vary depending on the child’s age: Children younger than 8 yr often have associated school refusal and excessive fear that harm will come to a parent; children 9-12 yr have excessive distress when separated from a parent; and those 13-16 yr often have school refusal and physical complaints. SAD may be more likely to develop in children with lower levels of psychosocial maturity. Parents are often unable to be assertive in returning the child to school. Mothers of children with SAD often have a history of an anxiety disorder. In these cases, the pediatrician should screen for parental depression or anxiety. Often referral for parental treatment or family therapy is necessary before SAD and concomitant school refusal can be successfully treated.

Comorbidity is common in SAD. In children with comorbid tic disorders and anxiety, SAD is especially associated with tic severity. SAD is a predictor for early onset of PD. Children with SAD compared to those without SAD are 3 times more likely to develop PD in adolescence.

When a child reports recurring acute severe anxiety, antidepressant or anxiolytic medication is often necessary. Controlled studies of tricyclic antidepressants (imipramine) and benzodiazepines (clonazepam) show that these agents are not generally effective. Data support the use of cognitive-behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) (see Table 21-4 in Chapter 21). One study of children 7-17 yr of age with a primary diagnosis of SAD compared 12 wk of treatment with CBT, the SSRI sertraline, their combination, and placebo. Nearly 81% of those treated with combination therapy improved, 55% for SSRI alone, 60% for CBT. All treatments were superior to placebo (24% response rate). The SSRI was well tolerated and had few side effects; adverse events, including suicidal and homicidal ideation, did not differ between the SSRI and placebo groups and there were no attempted suicides. CBT was associated with less insomnia, fatigue, sedation, and restlessness than SSRI. Combining SSRI with CBT may be the best approach to achieving a positive response; long-term SSRI treatment can provide additional benefit. Findings from this study are consistent with a meta-analysis of published and unpublished randomized controlled trials of antidepressants for pediatric patients with SAD, social phobia, or GAD.

Childhood-onset social phobia (social anxiety disorder) is characterized by excessive anxiety in social settings (including the presence
of unfamiliar peers, or unfamiliar adults) or performance situations, leading to social isolation (Table 25-2) and is associated with social scrutiny and fear of doing something embarrassing. Fear of social settings can also occur in other disorders, such as GAD. Avoidance or escape from the situation usually dissipates anxiety in social phobia (SP), unlike GAD, where worry persists. Children and adolescents with SP often maintain the desire for involvement with family and familiar peers. When severe, the anxiety can manifest as a panic attack.

SP is associated with a decreased quality of life, with increased likelihood of having failed at least 1 grade, and a 38% likelihood of not graduating from high school. Its onset is typically during or before adolescence and is more common in girls. A family history of SP or extreme shyness is common. Approximately 70-80% of patients with SP have at least 1 comorbid psychiatric disorder. Most shy patients do not have a SP.

Social effectiveness therapy for children (SET-C), alone or with SSRIs, is considered the treatment of choice for SP (see Table 21-4 in Chapter 21). SSRIs and SET-C are superior to placebo in reducing social distress and behavioral avoidance and increasing general functioning. SET-C may be better than SSRIs in reducing these symptoms. SET-C, but not SSRIs, may be superior to placebo in improving social skills, decreasing anxiety in specific social interactions, and enhancing social competence. SSRIs have a maximum effect by 8 wk; SET-C provides continued improvement through 12 wk. A combination of SSRIs and CBT is superior to either treatment alone in reducing severity of anxiety in children with SP and other anxiety disorders. β-Adrenergic blocking agents are used to treat SP, particularly the subtype with performance anxiety and stage fright. β-Blockers are not FDA approved for SP.

School refusal, which occurs in approximately 1-2% of children, is associated with anxiety in 40-50% of cases, depression in 50-60% of cases, and oppositional behavior in 50% of cases. Younger anxious children who refuse to attend school are more likely to have SAD, whereas older anxious children usually refuse to attend school because of SP. Somatic symptoms, especially abdominal pain and/or headaches, are common. There may be increasing tension in the parent–child relationship or other indicators of family disruption (domestic violence, divorce, or other major stressors) contributing to school refusal.

Management of school refusal typically requires parent management training and family therapy. Working with school personnel is always indicated; anxious children often require special attention from teachers, counselors, or school nurses. Parents who are coached to calmly send the child to school and to reward the child for each completed day of school are usually successful. In cases of ongoing school refusal, referral to a child and adolescent psychiatrist and psychologist is indicated. SSRI treatment may be helpful. Young children with affective symptoms have a good prognosis, whereas adolescents with more insidious onset or with significant somatic complaints have a more guarded prognosis.

Selective mutism is conceptualized as a disorder that overlaps with SP. Children with selective mutism talk almost exclusively at home, although they are reticent in other settings, such as school, daycare, or even relatives’ homes. The mutism must be present for ≥1 mo. Often, 1 or more stressors, such as a new classroom or conflicts with parents or siblings, drive an already shy child to become reluctant to speak. It may be helpful to obtain history of normal language use in at least 1 situation to rule out any communication disorder (fluency disorder), neurologic disorder, or pervasive developmental disorder (autism, schizophrenia) as a cause of mutism. Fluoxetine in combination with behavioral therapy is effective for children whose school performance is severely limited by their symptoms (see Chapter 35). Other SSRIs may also be effective.

PD is a syndrome of recurrent, discrete episodes of marked fear or discomfort in which patients experience abrupt onset of physical and psychologic symptoms called panic attacks (Table 25-3). Physical symptoms can include palpitations, sweating, shaking, shortness of breath, dizziness, chest pain, and nausea. Children can present with acute respiratory distress but without fever, wheezing, or stridor, ruling out organic causes of the distress. The associated psychologic symptoms include fear of death, impending doom, loss of control, persistent concerns about having future attacks, and avoidance of settings where attacks have occurred (agoraphobia, Table 25-4).

PD is uncommon before adolescence, with the peak age of onset at 15-19 yr of age, occurring more often in girls. The postadolescence prevalence of PD is 1-2%. Early-onset PD and adult-onset PD do not differ in symptom severity or social functioning. Early-onset PD is associated with greater comorbidity, which can result from greater familial loading for anxiety disorders in the early-onset subtype. Children of parents with PD are much more likely to develop PD. A prescription procedure to react to autonomic arousal with anxiety may be a specific risk factor leading to PD. Twin studies suggest that 30-40% of the variance is attributed to genetics. The increasing rates of panic attack are also directly related to earlier sexual maturity. Cued panic attacks can be present in other anxiety disorders and differ from the uncued “out-of-the-blue” attacks in PD.

No randomized controlled trials have evaluated the effectiveness of antidepressant medication in youth with PD. Open-label studies with SSRIs appear to show effectiveness in the treatment of adolescents (see Table 21-4 in Chapter 21). CBT may also be helpful. The recovery rate is approximately 70%.

GAD occurs in children who often experience unrealistic worries about different events or activities for at least 6 mo (Table 25-5) with at least 1 somatic complaint. The diffuse nature of the anxiety symptoms differentiates it from other anxiety disorders. Worries in children with GAD commonly center around concerns about competence and performance in school and athletics. GAD often manifests with somatic symptoms including restlessness, fatigue, problems concentrating, irritability, muscle tension, and sleep disturbance. Given the somatic

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**Table 25-2 DSM-5 Diagnostic Criteria for Social Anxiety Disorder (Social Phobia)**

**Diagnostic Criteria**

A. Marked fear or anxiety about 1 or more social situations in which the individual is exposed to possible scrutiny by others. Examples include social interactions (e.g., having a conversation, meeting unfamiliar people), being observed (e.g., eating or drinking), and performing in front of others (e.g., giving a speech).

B. The individual fears that he or she will act in a way or show anxiety symptoms that will be negatively evaluated (i.e., will be humiliating or embarrassing; will lead to rejection or offend others).

C. The social situations almost always provoke fear or anxiety.

**Note:** In children, the fear or anxiety may be expressed by crying, tantrums, freezing, clinging, shrinking, or failing to speak in social situations.

D. The social situations are avoided or endured with intense fear or anxiety.

E. The fear or anxiety is out of proportion to the actual threat posed by the social situation and to the sociocultural context.

F. The fear, anxiety, or avoidance is persistent, typically lasting for 6 mo or more.

G. The fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

H. The fear, anxiety, or avoidance is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

I. The fear, anxiety, or avoidance is not better explained by the symptoms of another mental disorder, such as panic disorder, body dysmorphic disorder, or autism spectrum disorder.

J. If another medical condition (e.g., Parkinson disease, obesity, disfigurement from burns or injury) is present, the anxiety or avoidance is clearly unrelated or is excessive.

**Specify if:**

**Performance only:** If the fear is restricted to speaking or performing in public.

### DSM-5 Diagnostic Criteria for Panic Disorder

A. Recurrent unexpected panic attacks. A panic attack is an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes, and during which time 4 (or more) of the following symptoms occur:

**Note:** The abrupt surge can occur from a calm state or an anxious state.

1. Palpitations, pounding heart, or accelerated heart rate.
2. Sweating
3. Trembling or shaking.
4. Sensations of shortness of breath or smothering.
5. Feelings of choking.
6. Chest pain or discomfort.
7. Nausea or abdominal distress.
9. Chills or heart sensations.
10. Paresthesias (numbness or tingling sensations).
11. Derealizations (feeling or unreality) or depersonalization (being detached from one-self).
12. Fear of losing control or “going crazy.”

**Note:** Culture-specific symptoms (e.g., tinnitus, neck soreness, headache, uncontrollable screaming or crying) may be seen. Such symptoms should not count as 1 of the 4 required symptoms.

B. At least 1 of the attacks has been followed by 1 mo (or more) of 1 or both of the following:

1. Persistent concern or worry about additional panic attacks or their consequences (e.g., losing control, having a heart attack, “going crazy”).
2. A significant maladaptive change in behavior related to the attacks (e.g., behaviors designed to avoid having panic attacks, such as avoidance of exercise or unfamiliar situations).

C. The disturbance is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hypothyroidism, cardiopulmonary disorders).

D. The disturbance is not better explained by another mental disorder (e.g., the panic attacks do not occur only in response to feared social situations, as in social anxiety disorder; in response to circumscribed phobic objects or situations, as in specific phobia; in response to obsessions, as in obsessive-compulsive disorder; or in response to reminders of traumatic events, as in posttraumatic stress disorder; or in response to separation from attachment figures, as in separation anxiety disorder).

### DSM-5 Diagnostic Criteria for Agoraphobia

A. Marked fear or anxiety about 2 (or more) of the following 5 situations:

1. Using public transportation (e.g., automobiles, buses, trains, ships, planes).
2. Being in open spaces (e.g., parking lots, marketplaces, bridges).
3. Being in enclosed places (e.g., shops, theaters, cinemas).
4. Standing in line or being in a crowd.
5. Being outside of the home alone.

**B.** The individual fears or avoids these situations because of thoughts that escape might be difficult or help might not be available in the event of a developing panic-like symptoms or other incapacitating or embarrassing symptoms (e.g., fear or falling in the elderly, fear of incontinence).

**C.** The agoraphobic situations almost always provoke fear or anxiety.

**D.** The agoraphobic situations are actively avoided, require the presence of a companion, or are endured with intense fear or anxiety.

**E.** The fear or anxiety is out of proportion to the actual danger posed by the agoraphobic situations and to the sociocultural context.

**F.** The fear, anxiety, or avoidance is persistent, typically lasting for 6 mo or more.

**G.** The fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational or other important area of functioning.

**H.** If another medical condition (e.g., inflammatory bowel disease, Parkinson disease) is present, the fear, anxiety, or avoidance is clearly excessive.

**I.** The fear, anxiety, or avoidance is not better explained by the symptoms or another mental disorder—for example, the symptoms are not confined to specific phobia, situational type; do not involve only social situations (as in social anxiety disorder); and are not related exclusively to obsessions (as in obsessive-compulsive disorder), reminders or traumatic events (as in posttraumatic stress disorder), or fear of separation (as in separation anxiety disorder).

**Note:** Agoraphobia is diagnosed irrespective of the presence of panic disorder. If an individual’s presentation meets criteria for panic disorder and agoraphobia, both diagnoses should be assigned.

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It is important to distinguish children with GAD from those who present with specific repetitive thoughts that invade consciousness (obsessions) or repetitive rituals or movements that are driven by anxiety (compulsions). The most common obsessions are concerned with bodily wastes and secretions, the fear that something calamitous will happen, or the need for sameness. The most common compulsions are hand washing, continual checking of locks, and touching. At times of stress (bedtime, preparing for school), some children touch certain objects, say certain words, or wash their hands repeatedly. OCD is diagnosed when the thoughts or rituals cause distress, consume time, or interfere with occupational or social functioning (Table 25-6). In the DSM-5, OCD and related disorders (such as trichotillomania, excoriation, body dysmorphic disorder, and hoarding) are listed separately and are no longer included under anxiety disorders.

OCD is a chronically disabling illness characterized by repetitive, ritualistic behaviors over which the patient has little or no control. OCD has a lifetime prevalence of 1-3% worldwide, and as many as 80% of all cases have their onset in childhood and adolescence. Common obsessions include contamination (35%) and thoughts of harming loved ones or oneself (30%). Washing and cleaning compulsions are common in children (75%), as are checking (40%) and straightening (35%). Many children are observed to have visuospatial irregularities, memory problems, and attention deficits, causing academic problems not explained by OCD symptoms alone.
Part III  Behavioral and Psychiatric Disorders

Table 25-5  DSM-5 Diagnostic Criteria for Generalized Anxiety Disorder

<table>
<thead>
<tr>
<th>A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 mo, about a number of events or activities (such as work or school performance).</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. The individual finds it difficult to control the worry.</td>
</tr>
<tr>
<td>C. The anxiety and worry are associated with 3 (or more) of the following 6 symptoms (with at least some symptoms having been present for more days than not for the past 6 mo):</td>
</tr>
</tbody>
</table>

Note: Only 1 item is required in children.

1. Restlessness or feeling keyed up or on edge.
2. Being easily fatigued.
3. Difficulty concentrating or mind going blank.
4. Irritability.
5. Muscle tension.
6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).

D. The anxiety, worry or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

E. The disturbance is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or other medical condition (e.g., hyperthyroidism).

F. The disturbance is not better explained by another mental disorder (e.g., anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder (social phobia), contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, remainders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder).

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 222.

Table 25-6  DSM-5 Diagnostic Criteria for Obsessive-Compulsive Disorder

<table>
<thead>
<tr>
<th>A. Presence of obsessions, compulsions, or both:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obsessions are defined by (1) and (2):</td>
</tr>
<tr>
<td>1. Recurrent and persistent thoughts, urges, or images that are experienced, at some time during the disturbance, as intrusive and unwanted, and that in most individuals cause marked anxiety or distress.</td>
</tr>
<tr>
<td>2. The individual attempts to ignore or suppress such thoughts, urges or images, or to neutralize them with some other thought or action (i.e., by performing a compulsion).</td>
</tr>
<tr>
<td>Compulsions are defined by (1) and (2):</td>
</tr>
<tr>
<td>1. Repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly.</td>
</tr>
<tr>
<td>2. The behaviors or mental acts are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviors or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly excessive.</td>
</tr>
</tbody>
</table>

B. The obsessions or compulsions are time-consuming (e.g., take more than 1 hr per day) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The obsessive-compulsive symptoms are not attributable to the psychologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

D. The disturbance is not better explained by the symptoms of another mental disorder (e.g., excessive worries, as in generalized anxiety disorder; preoccupation with appearance, as in body dysmorphic disorder; difficulty discarding or parting with possessions, as in hoarding disorder; hair pulling, as in trichotillomania [hair-pulling disorder]; skin picking, as in excoriation [skin-picking] disorder; stereotypies, as in stereotypic movement disorder; ritualized eating disorder, as in eating disorders; preoccupation with substances or gambling, as in substance-related and addictive disorders; preoccupation with having an illness, as in illness anxiety disorder; sexual urges or fantasies, as in paraphilic disorders; impulses, as in disruptive, impulse-control and conduct disorders; guilty ruminations, as in schizophrenia spectrum and other psychotic disorders; or repetitive patterns of behavior, as in autism spectrum disorder).

Specify if: |
| With good or fair insight: The individual recognizes that obsessive-compulsive disorder beliefs are definitely or probably not true or that they may or may not be true. |
| With poor insight: The individual thinks obsessive-compulsive disorder beliefs are probably true. |
| With absent insight/delusional beliefs: The individual is completely convinced that obsessive-compulsive disorder beliefs are true. |

Specify if: |
| Tic-related: The individual has a current or past history of a tic disorder. |


The Children’s Yale-Brown Obsessive-Compulsive Scale (C-YBOCS) and the Anxiety Disorders Interview Schedule for Children (ADIS-C) are reliable and valid methods for identifying children with OCD. The C-YBOCS is helpful in following the progression of symptoms with treatment. The Leyton Obsessional Inventory (LOI) is a self-report measure of OCD symptoms that is quite sensitive. Patients with OCD have consistently identified abnormalities in the frontostriatal-thalamic circuitry associated with severity of illness and treatment response. Comorbidity is common in OCD, with 30% of patients having comorbid tic disorders, 26% having comorbid major depression, and 24% having comorbid developmental disorders.

Consensus guidelines recommend that children and adolescents with OCD begin treatment with either CBT alone or CBT in combination with SSRIs, when symptoms are moderate to severe (YBOCS >21). In OCD patients with comorbid tics, SSRIs are no more effective than placebo, and combination of CBT and SSRI is superior to CBT; CBT alone is superior to placebo. Pediatric OCD patients with comorbid tics should begin treatment with CBT alone or the combination of CBT and SSRI. Pediatric patients with OCD who have a family history of OCD may be significantly less responsive to CBT alone than patients without a family history of OCD.

There are 4 FDA-approved medications for pediatric OCD: fluoxetine, sertraline, fluvoxamine, and clomipramine. Clomipramine, a tricyclic antidepressant and nonselective serotonin and norepinephrine reuptake inhibitor, is only indicated when a patient has failed 2 or more SSRI trials. There may be a role for glutamate-modulating medications in the treatment of OCD. The glutamate inhibitorriluzole (Rilutek) is FDA-approved for amyotrophic lateral sclerosis (see Chapter 612.3) and has a good safety record. The most common adverse event withriluzole is transient increase in liver transaminases. Riluzole in children with treatment-resistant OCD may be beneficial and is well tolerated. Other glutamate-modulating agents, such as memantine, N-acetyl-cysteine, and d-cycloserine, have been used with some success in patients with OCD. Referral of patients with OCD to a mental health professional is always indicated.

In 10% of children with OCD, symptoms are triggered or exacerbated by group A β-hemolytic streptococcal infection (see Chapter 183). Group A β-hemolytic streptococcal bacteria trigger antineuronal antibodies that cross-react with basal ganglia neural tissue in genetically susceptible hosts, leading to swelling of this region and resultant obsessions and compulsions. This subtype of OCD, called pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS), is characterized by sudden and dramatic onset or exacerbation of OCD or tic symptoms, associated neurologic findings, and a recent streptococcal infection. Increased
antibody titers of antistreptolysin O and antideoxyribonuclease B correlates with increased basal ganglia volumes. Plasmapheresis is effective in reducing OCD symptoms in some patients with PANDAS and also decreasing enlarged basal ganglia volume. OCD has also followed episodes of acute disseminated encephalomyelitis (see Chapter 600.3). The pediatrician should be aware of the infectious cause of some cases of tic disorders, attention-deficit disorder, and OCD and follow management guidelines (see Chapter 24). Children with phobias avoid specific objects or situations that reliably trigger physiologic arousal (e.g., dogs or spiders) (see Table 25-1). The fear is excessive and unreasonable and can be cured by the presence or anticipation of the feared trigger, with anxiety symptoms occurring immediately. Neither obsessions nor compulsions are associated with the fear response; phobias only rarely interfere with social, educational, or interpersonal functioning. Assault by a relative and verbal aggression between parents can influence the onset of specific phobias. The parents of phobic children should remain calm in the face of the child’s anxiety or panic. Parents who become anxious themselves may reinforce their child’s anxiety, and the pediatrician can usefully interrupt this cycle by calmly noting that phobias are not unusual and rarely cause impairment. The prevalence of specific phobias in childhood is 0.5-2%. Systematic desensitization is a form of behavior therapy that gradually exposes the patient to the fear-inducing situation or object, while simultaneously teaching relaxation techniques for anxiety management. Successful repeated exposure leads to extinguishing anxiety for that stimulus. When phobias are particularly severe, SSRIs can be used with behavioral intervention. Low-dose SSRI treatment may be especially effective for some children with severe, refractory choking phobia. PTSD (see Chapter 39) is typically precipitated by an extreme stressor. PTSD is an anxiety disorder resulting from the long- and short-term effects of trauma that cause behavioral and physiologic sequelae in toddlers, children, and adolescents (Table 25-7). Another

<table>
<thead>
<tr>
<th>Table 25-7</th>
<th>DSM-5 Diagnostic Criteria for Posttraumatic Stress Disorder</th>
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<tbody>
<tr>
<td><strong>POSTTRAUMATIC STRESS DISORDER</strong></td>
<td>Note: The following criteria apply to adults, adolescents, and children older than 6 yr. For children 6 yr and younger, see corresponding criteria below.</td>
</tr>
<tr>
<td>A. Exposure to actual or threatened death, serious injury, or sexual violence in 1 (or more) of the following ways:</td>
<td>1. Directly experiencing the traumatic event(s).</td>
</tr>
<tr>
<td>B. Witnessing, in person, the event(s) as it occurred to others.</td>
<td>2. Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental.</td>
</tr>
<tr>
<td>C. Hearing about the event(s) in a violent or die manner (e.g., descriptions by others).</td>
<td>4. Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., 1st responders collecting human remains; police officers repeatedly exposed to details of child abuse).</td>
</tr>
<tr>
<td><strong>Note:</strong> Criterior A4 does not apply to exposure through electronic media, television, movies or pictures, unless this exposure is work related.</td>
<td><strong>Note:</strong> In children older than 6 yr, repetitive play may occur in which themes or aspects of the traumatic event(s) are expressed.</td>
</tr>
<tr>
<td>D. Presence of 1 (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:</td>
<td>1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s).</td>
</tr>
<tr>
<td>E. Recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s).</td>
<td><strong>Note:</strong> In children, there may be frightening dreams without recognizable content.</td>
</tr>
<tr>
<td>F. Notice of 1 (or more) of the following negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred:</td>
<td>3. Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the more extreme expression being a complete loss or awareness of present surroundings.)</td>
</tr>
<tr>
<td><strong>Note:</strong> In children, trauma-specific reenactment may occur in play.</td>
<td><strong>Note:</strong> In children, trauma-specific reenactment may occur in play.</td>
</tr>
<tr>
<td>1. Avoidance of or efforts to avoid distressing memories, thoughts or feelings about or closely associated with the traumatic event(s).</td>
<td>4. Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).</td>
</tr>
<tr>
<td>2. Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts or feelings about or closely associated with the traumatic event(s).</td>
<td>5. Marked physiologic reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).</td>
</tr>
<tr>
<td>D. Negative alterations in cognition and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by 2 (or more) of the following:</td>
<td>C. Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by 1 or both of the following:</td>
</tr>
<tr>
<td>1. Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs).</td>
<td>1. Avoidance of or efforts to avoid distressing memories, thoughts or feelings about or closely associated with the traumatic event(s).</td>
</tr>
<tr>
<td>2. Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., “I am bad,” “No one can be trusted.” “The world is completely dangerous,” “My whole nervous system is permanently ruined”).</td>
<td>2. Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts or feelings about or closely associated with the traumatic event(s).</td>
</tr>
<tr>
<td>E. Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by 2 (or more) of the following:</td>
<td>3. Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the more extreme expression being a complete loss or awareness of present surroundings.)</td>
</tr>
<tr>
<td>1. Irritable behavior and angry outbursts (with little or no provocation) typically expressed by verbal or physical aggression toward people or objects.</td>
<td><strong>Note:</strong> In children, trauma-specific reenactment may occur in play.</td>
</tr>
<tr>
<td>2. Reckless or self-destructive behavior.</td>
<td>4. Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).</td>
</tr>
<tr>
<td>3. Hypervigilance.</td>
<td>5. Marked physiologic reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).</td>
</tr>
<tr>
<td>4. Exaggerated startle response.</td>
<td>6. Feelings of detachment or estrangement from others.</td>
</tr>
<tr>
<td>5. Problems with concentration.</td>
<td>7. Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings).</td>
</tr>
<tr>
<td>6. Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep).</td>
<td>F. Duration of the disturbance (Criteria B, C, D, and E) is more than 1 mo.</td>
</tr>
<tr>
<td>G. The disturbance causes clinically significant distress or impairment in social, occupational or other important areas of functioning.</td>
<td>H. The disturbance is not attributable to the physiologic effects of a substance (e.g., medication, alcohol) or another medical condition.</td>
</tr>
</tbody>
</table>
Table 25-7  DSM-5 Diagnostic Criteria for Posttraumatic Stress Disorder—cont’d

Specify whether

With dissociative symptoms: The individual’s symptoms meet the criteria for posttraumatic stress disorder, and in addition, in response to the stressor, the individual experiences persistent or recurrent symptoms of either of the following:

1. **Depersonalization**: Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one’s mental processes or body (e.g., feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).
2. **Derealization**: Persistent or recurrent experiences of unreality of surroundings (e.g., the world around the individual is experienced as unreal, dreamlike, distant, or distorted).

Note: to use this subtype, the dissociative symptoms must not be attributable to the physiologic effects of a substance (e.g., blackouts, behavior during alcohol intoxication) or another medical condition (e.g., complex partial seizures). Specify if:

With delayed expression: If the full diagnostic criteria are not met until at least 6 mo after the event (although the onset and expression of some symptoms may be immediate).

**POSTTRAUMATIC STRESS DISORDER FOR CHILDREN 6 YR AND YOUNGER**

A. In children 6 yr and younger, exposure to actual or threatened death, serious injury, or sexual violence in 1 (or more) of the following ways:
1. Directly experiencing the traumatic event(s).
2. Witnessing, in person, the event(s) as it occurred to others, especially primary caregivers.

Note: Witnessing does not include events that are only in electronic media, television, movies, or pictures.
3. Learning that the traumatic event(s) occurred to a parent or caregiving figure.

B. Presence of 1 (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:
1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s).
2. Recurrent distressing dreams in which the content and/or affect of the dream is related to the traumatic event(s).
3. Dissociative reactions (e.g., flashbacks) in which the child feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.) Such trauma-specific reenactment may occur in play.
4. Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

C. One (or more) of the following symptoms, representing either persistent avoidance of stimuli associated with the traumatic event(s) or negative alterations in cognitions and mood associated with the traumatic event(s), must be present, beginning after the event(s) or worsening after the event(s):

**Persistent Avoidance of Stимuli**
1. Avoidance of or efforts to avoid activities, places, or physical reminders that arouse recollections of the traumatic event(s).
2. Avoidance of or efforts to avoid people, conversations, or interpersonal situations that around recollections of the traumatic event(s).

**Negative Alterations in Cognitions**
3. Substantially increased frequency of negative emotional states (e.g., fear, guilt, sadness, shame, confusion).
4. Markedly diminished interest or participation in significant activities, including constriction of play.
5. Socially withdrawn behavior.
6. Persistent reduction in expression of positive emotions.

D. Alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by 2 (or more) of the following:
1. Irritable behavior and angry outbursts (with little or no provocation), typically expressed as verbal and physical aggression toward people or objects (including extreme temper tantrums).
2. Hypervigilance.
3. Exaggerated startle response.
4. Problems with concentration.
5. Sleep disturbance (e.g., difficulty falling asleep or staying asleep or restless sleep).

E. The duration of the disturbance is more than 1 mo.
F. The disturbance causes clinically significant distress or impairment in relationships with parents, siblings, peers, or other caregivers or with school behavior.

G. The disturbance is not attributable to the physiologic effects of a substance (e.g., medication or alcohol) or another medical condition.

Specify whether:

With dissociative symptoms: The individual’s symptoms meet the criteria for posttraumatic stress disorder, and the individual experiences persistent or recurrent symptoms of either of the following:

1. **Depersonalization**: Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one’s mental processes or body (e.g., feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).
2. **Derealization**: Persistent or recurrent experiences of unreality of surroundings (e.g., the world around the individual is experienced as unreal, dreamlike, distant, or distorted).

Note: to use this subtype, the dissociative symptoms must not be attributable to the physiologic effects of a substance (e.g., blackouts, behavior during alcohol intoxication) or another medical condition (e.g., complex partial seizures). Specify if:

With delayed expression: If the full diagnostic criteria are not met until at least 6 mo after the event (although the onset and expression of some symptoms may be immediate).

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, pp. 271-274.
diagnostic category, **acute stress disorder**, reflects the fact that traumatic events often cause acute symptoms that may or may not resolve. Previous trauma exposure, a history of other psychopathology, and symptoms of PTSD in parents predict childhood-onset PTSD. Many adolescent and adult psychopathologic conditions, such as conduct disorder, depression, and some personality disorders, might relate to previous trauma. PTSD is also linked to mood disorders and disruptive behavior. Separation anxiety is common in children with PTSD. The lifetime prevalence of PTSD by age 18 yr is approximately 6%. Up to 40% show symptoms, but do not fulfill the diagnostic criteria.

Events that pose physical injury, harm, or death to the child, to the child’s caregiver, or to others close to the child and that produce considerable stress, fear, and/or helplessness are required to make the diagnosis of PTSD. Three clusters of symptoms are also essential for diagnosis: reexperiencing, avoidance, and hyperarousal. Persistent reexperiencing of the stressor through intrusive recollections, nightmares, and reenactment in play are typical responses in children. Persistent avoidance of reminders and numbing of emotional responsiveness, such as isolation, amnesia, and avoidance, constitute the second cluster of behaviors. Symptoms of hyperarousal, such as hypervigilance, poor concentration, extreme startle responses, agitation, and sleep problems, complete the symptom profile of PTSD. Occasionally, children regress in some of their developmental milestones after a traumatic event. Avoidance symptoms are commonly observable in younger children, whereas older children may be more able to describe reexperiencing and hyperarousal symptoms. Repetitive play involving the event, psychosomatic symptoms, and nightmares may also be observed.

Initial interventions after a trauma should focus on reunification with a parent and attending to the child’s physical needs in a safe place. Aggressive treatment of pain might decrease the likelihood of PTSD, and facilitating a return to comforting routines, including regular sleep, is indicated. Long-term treatment may include individual, group, school-based, or family therapy, as well as pharmacotherapy, in selected cases. Individual treatment involves transforming the child’s concept of himself or herself as victim to that of survivor and can occur through play therapy, psychodynamic therapy, or CBT. Group work is also helpful for identifying which children might need more intensive assistance. Goals of family work include helping the child establish a sense of security, validating the child’s emotions, and anticipating situations when the child will need more support from the family. Clonidine or guanfacine may be helpful for sleep disturbance, persistent arousal, and exaggerated startle response. Recent randomized controlled trials in children and adolescents with PTSD did not find a significant difference between SSRI and placebo. SSRIs may be considered in pediatric patients with PTSD who have comorbid conditions responsive to SSRIs, for example, depression, affective numbing, and anxiety (see Table 21.4 in Chapter 21). As for many other anxiety disorders, CBT is the psychotherapeutic intervention with the most empiric support.

**ANXIETY ASSOCIATED WITH MEDICAL CONDITIONS**

It is prudent to rule out organic conditions such as hyperthyroidism, caffeineism (carbonated beverages), hypoglycemia, central nervous system disorders (delirium, encephalopathy, brain tumors), migraine, asthma, lead poisoning, cardiac arrhythmias, and, rarely, pulmonary embolism, hyperparathyroidism, systemic lupus erythematosus, anaphylaxis, porphyria or pheochromocytoma, before making a diagnosis of an anxiety disorder. Some prescription drugs with side effects that can mimic anxiety include antiasthmatic agents, steroids, sympathomimetics, SSRIs (initiation), anticholinergic agents, and antipsychotics. Nonprescription drugs causing anxiety include diet pills, antihistamines, stimulate drugs of abuse, drug withdrawal, and cold medicines.

Chronic illness is also an underlying cause of anxiety. Children are not often emotionally and cognitively competent to understand the implications of a serious and prolonged illness. In addition to the physiologic implications of illness they must also attend to the hospitalizations, procedures and medications that permeate their everyday schedule. This experience affects their schooling, friendships, activities, and dynamics of the nuclear family including the experiences of their well siblings.

School issues surrounding both prolonged absences and school re-entry following a medical condition can cause, or reinforce and escalate existing anxiety. School is a foundation not only for learning, but it is central to children’s social experiences and feelings of normalcy. It is often impeded and stunted by illness. Academic struggles can result from missing classes, medication and emotional status. Children with chronic conditions are also socially disadvantaged with friendship networks hampered by unstable attendance or by social rejection for being different. Consulting with the school psychologist can be beneficial in preparing teachers and classmates before the child returns to school. An agreement between the student and school staff should be implemented outlining a plan for taking medication, needing rest or consulting on other needs. If the child and family wish, an informational meeting with students and teachers can normalize the situation. Explaining the condition makes it less scary for children who catastrophize or worry about contagion. Classmates and teachers are a natural and accessible resource and can be an incredible support and community. Medication may also be warranted to supplement social supports.

The experiences of the siblings of children with chronic illness are often forgotten with familial resources focused on medical and financial consequences, and the emotional and physical functioning of the ill child. It is not uncommon for the siblings of ill children to experience depression and anxiety as well. Assessing their social support systems, communication opportunities with parents and emotional outlets are critical to maintaining healthy functioning. Maintaining a redefined schedule of after-school activities and social engagements are helpful in allowing siblings to continue in school.

**SAFETY AND EFFICACY CONCERNS ABOUT SSRIS**

No empiric evidence suggests the superiority of one SSRI over another. Data are limited as far as combining medications are concerned. SSRIs are usually well tolerated by most children and adolescents. The FDA issued a black box warning of increased agitation and suicidality among adolescents and children on these medications. This warning was based on review of studies in children and adolescents with major depression and not anxiety disorders. Close monitoring is always warranted.

*Bibliography is available at Expert Consult.*
### Bibliography


Mood disorders are interrelated sets of psychiatric symptoms characterized by a core deficit in emotional self-regulation. Classically, the mood disorders have been divided into depressive and bipolar disorders, representing the 2 emotional polarities (dysphoric ["low"] and euphoric ["high"] mood).

26.1 Major and Other Depressive Disorders

The depressive disorders include major depressive, persistent depressive, disruptive mood dysregulation, other specified/unspecified
depressive, premenstrual dysphoric, and substance/medication-induced disorders, as well as depressive disorder caused by another medical condition.

**DESCRIPTION**

Major depressive disorder (MDD) is characterized by a distinct period of at least 2 wk (an episode; Table 26-1) in which there is a depressed or irritable mood and/or loss of interest or pleasure in almost all activities most of the day, nearly every day. Major depression is considered to be mild if few or no symptoms of depression are present, and the symptoms are mildly distressing and manageable and result in minor functional impairment. Major depression is considered to be severe if symptoms substantially in excess of those required to make the diagnosis are present, and the symptoms are highly distressing and unmanageable and markedly impair function. Moderate major depression is intermediate in severity between mild and severe.

Persistent depressive disorder (dysthymia) (Table 26-2) is characterized by depressed or irritable mood for more than 2 yr (1 yr for children and adolescents). As with major depression, this chronic form of depression is associated with characteristic vegetative and cognitive symptoms; however, the cognitive symptoms of persistent depression are less severe (e.g., low self-esteem rather than worthlessness, hopelessness rather than suicidality). In the same way as major depression, persistent depressive disorder is characterized as mild, moderate, or severe.

Overall, the clinical presentation of major and persistent depressive disorders in children and adolescents is similar to that in adults. The prominence of the symptoms can change with age: irritability and somatic complaints may be more common in children, and energy, activity level, appetite, and sleep disturbances may be more common in adolescents. Because of the cognitive and linguistic immaturities of young children, symptoms of depression in that age group may be more likely to be observed than self-reported.

The core feature of disruptive mood dysregulation disorder (DMDD) (Table 26-3) is severe, persistent irritability evident for at least 12 mo in multiple settings (at home, at school, with peers). This irritability is characterized by frequent and severe temper outbursts (verbal and/or physical) and a persistently irritable or angry mood that is present for most of the day, nearly every day. This diagnosis is intended to more accurately characterize the extreme irritability heretofore considered by some investigators to be a developmental presentation of bipolar disorder (see Chapter 26.2), and to distinguish extreme irritability from the milder presentations characteristic of oppositional defiant and intermittent explosive disorders (see Chapter 29).

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**Table 26-1 DSM-5 Diagnostic Criteria for Major Depressive Episode**

<table>
<thead>
<tr>
<th>A. Five (or more) of the following symptoms have been present during the same 2 wk period and represent a change from previous functioning; at least 1 of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Depressed most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). <strong>Note:</strong> In children and adolescents, can be irritable mood.</td>
</tr>
<tr>
<td>2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).</td>
</tr>
<tr>
<td>3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. <strong>Note:</strong> In children, consider failure to make expected weight gain.</td>
</tr>
<tr>
<td>4. Insomnia or hypersomnia nearly every day.</td>
</tr>
<tr>
<td>5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).</td>
</tr>
<tr>
<td>6. Fatigue or loss of energy nearly every day.</td>
</tr>
<tr>
<td>7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).</td>
</tr>
<tr>
<td>8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).</td>
</tr>
<tr>
<td>9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.</td>
</tr>
</tbody>
</table>

**B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.**

**C. The episode is not attributable to the physiological effects of a substance or to another medical condition.**

**Note:** Criteria A-C represent a major depressive episode.

**D. The occurrence of the major depressive episode is not better explained by a persistent schizoaffective disorder, schizophrenia, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder.**

**E. There has never been a manic episode or a hypomanic episode.**

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**Table 26-2 DSM-5 Diagnostic Criteria for Persistent Depressive Disorder**

<table>
<thead>
<tr>
<th>A. Depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for at least 2 yr. <strong>Note:</strong> In children and adolescents, mood can be irritability and duration must be at least 1 yr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. Presence, while depressed, of 2 (or more) of the following:</td>
</tr>
<tr>
<td>1. Poor appetite or overeating.</td>
</tr>
<tr>
<td>2. Insomnia or hypersomnia.</td>
</tr>
<tr>
<td>3. Low energy or fatigue.</td>
</tr>
<tr>
<td>4. Low self-esteem.</td>
</tr>
<tr>
<td>5. Poor concentration or difficulty making decisions.</td>
</tr>
<tr>
<td>6. Feelings of hopelessness.</td>
</tr>
<tr>
<td>C. During the 2 yr period (1 yr for children or adolescents) of the disturbance, the individual has never been without the symptoms in Criteria A and B for more than 2 mo at a time.</td>
</tr>
<tr>
<td>D. Criteria for a major depressive disorder may be continuously present for 2 yr.</td>
</tr>
<tr>
<td>E. There has never been a manic episode or a hypomanic episode, and criteria have never been met for cyclothymic disorder.</td>
</tr>
<tr>
<td>F. The disturbance is not better explained by a persistent schizoaffective disorder, schizophrenia, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder.</td>
</tr>
<tr>
<td>G. The symptoms are not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hypothyroidism).</td>
</tr>
<tr>
<td>H. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. <strong>Note:</strong> Because the criteria for a major depressive episode include 4 symptoms that are absent from the symptom list for persistent depressive disorder (dysthymia), a very limited number of individuals will have depressive symptoms that have persisted longer than 2 yr but will not meet criteria for persistent depressive disorder. If full criteria for a major depressive episode have been met at some point during the current episode of illness, they should be given a diagnosis of major depressive disorder. Otherwise, a diagnosis of other specified depressive disorder or unspecified depressive disorder is warranted.</td>
</tr>
</tbody>
</table>

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Table 26-3  DSM-5 Diagnostic Criteria for Disruptive Mood Dysregulation Disorder

A. Severe recurrent temper outbursts manifested verbally (e.g., verbal rages) and/or behaviorally (e.g., physical aggression toward people or property) that are grossly out of proportion in intensity or duration to the situation or provocation.
B. The temper outbursts are inconsistent with developmental level.
C. The temper outbursts occur, on average, 3 or more times per week.
D. The mood between temper outbursts is persistently irritable or angry most of the day, nearly every day, and is observable by others (e.g., parents, teachers, peers).
E. Criteria A-D have been present for 12 or more months. Throughout that time, the individual has not had a period lasting 3 or more consecutive months without all of the symptoms in Criteria A-D.
F. Criteria A and D are present in at least 2 of 3 settings (i.e., at home, at school, with peers) and are severe in at least 1 of these.
G. The diagnosis should not be made for the first time before age 6 yr or after age 18 yr.
H. By history or observation, the age at onset of Criteria A-E is before 10 yr.
I. There has never been a distinct period lasting more than 1 day during which the full symptom criteria, except duration, for a manic or hypomanic episode have been met.

Note: Developmentally appropriate mood elevation, such as occurs in the context of a highly positive event or its anticipation, should not be considered as a symptom of mania or hypomania.
J. The behaviors do not occur exclusively during an episode of major depressive disorder and are not better explained by another mental disorder (e.g., autism spectrum disorder, posttraumatic stress disorder, separation anxiety disorder, persistent depressive disorder [dysthymia]).

Note: The diagnosis cannot coexist with oppositional defiant disorder, intermittent explosive disorder, or bipolar disorder, though it can coexist with others, including major depressive disorder, attention-deficit/hyperactivity disorder, conduct disorder, and substance use disorders. Individuals whose symptoms meet criteria for both disruptive mood dysregulation disorder and oppositional defiant disorder should only be given the diagnosis of disruptive mood dysregulation disorder if an individual has ever experienced a manic or hypomanic episode, the diagnosis of disruptive mood dysregulation disorder should not be assigned.
K. The symptoms are not attributable to the physiologic effects of a substance or to another medical or neurologic condition.


Other specified/unspecified depressive disorder (subsyndromal depressive disorder) applies to presentations in which symptoms characteristic of a depressive disorder are present and cause clinically significant distress or functional impairment, but do not meet the full criteria for any of the disorders in this diagnostic class.

EPIDEMIOLOGY

The overall prevalence of parent-reported diagnosis of depressive disorder in the United States (excluding DMDD) among 3-17 yr old children is ~2.1% (current) and ~3.9% (ever); the prevalence rate increases to ~12.8% (lifetime) for 12-17 yr olds. The male:female ratio (excluding DMDD) approximates 1:1 during childhood and beginning in early adolescence rises to 1:1.5-3.0 in adulthood.

Based upon rates of chronic and severe persistent irritability, which is the core feature of DMDD, the overall 6 mo to 1 yr prevalence has been estimated to fall within the 2-5% range. In 3 community samples, the 3 mo prevalence rate of DMDD ranged from 0.8-3.3%, with the highest rates occurring in preschoolers. Approximately 5-10% of children and adolescents are estimated to have subsyndromal (unspecified) depression.

CLINICAL COURSE

Major depression may first appear at any age, but the likelihood of onset increases markedly with puberty. Incidence appears to peak in the 20s. The median duration of a major depressive episode approximates 5-8 mo for clinically referred youth and 3-6 mo for community samples. The course is quite variable in that some individuals rarely or never experience remission, whereas others experience many years with few or no symptoms between episodes. Persistent depressive disorder often has an early and insidious onset, and by definition, a chronic course (average untreated duration in both clinical and community samples: 3.5 yr).

Prepubertal depressive disorders exhibit more heterotopic than homotypic continuity; depressed children appear to be more likely to develop nondepressive psychiatric disorders in adulthood than depressive disorders. Adolescents exhibit greater homotypic continuity, with the probability of recurrence of depression reaching 50%-70% after 5 yr. The persistence of even mild depressive symptoms during remission is a powerful predictor of recurrence; other negative prognostic factors include more severe symptoms, longer time to remission, history of maltreatment, and comorbid psychiatric disorders. Up to 20% of depressed adolescents develop a bipolar disorder; the risk is higher among adolescents who have a high family loading for bipolar disorder, who have psychotic depression, or who have had pharmacologically induced mania.

DIFFERENTIAL DIAGNOSIS

A number of psychiatric disorders, general medical conditions, and medications can generate symptoms of depression or irritability and must be distinguished from the depressive disorders. The psychiatric disorders include autism spectrum (see Chapter 30), attention-deficit/hyperactivity (ADHD; see Chapter 33), bipolar, anxiety (see Chapter 25), trauma- and stressor-related, disruptive/impulse control/conduct, and substance-related disorders. Medical conditions include neurologic disorders, endocrine disorders, infectious diseases, tumors, anemia, uremia, failure to thrive, chronic fatigue disorder, and pain disorder. Medications include narcotics, chemotherapy agents, β-blockers, corticosteroids, and contraceptives. The diagnosis of a depressive disorder should be made after these other explanations for the observed symptoms have been ruled out.

COMORBIDITY

Major and persistent depressive disorders often co-occur with other psychiatric disorders. Depending on the setting and source of referral, 40-90% of youths with a depressive disorder have other psychiatric disorders, and up to 50% have 2 or more comorbid diagnoses. The most common comorbid diagnosis is an anxiety disorder and as such may reflect a common diathesis; other common comorbidities include ADHD and disruptive behavior, eating, and substance use disorders. The development of depressive disorders can both lead and follow the development of the comorbid disorders.

Preliminary data suggests the co-occurrence of DMDD with other psychiatric disorders, including other depressive disorders, ADHD, conduct disorder, and substance use disorders, from 60-90% of the time. Because the symptoms of DMDD overlap in part with symptoms of bipolar disorder (see Chapter 26.2), oppositional defiant disorder (see Chapter 29), and intermittent explosive disorder (see Chapter 29), by Diagnostic Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) convention hierarchical diagnostic rules apply (i.e., bipolar disorder takes precedence over DMDD if a manic/hypomanic episode has ever occurred; DMDD takes precedence over oppositional defiant disorder and intermittent explosive disorder if full criteria for DMDD are met).

SEQUELAE

Approximately 60% of youths with MDD report thinking about suicide, and 30% actually attempt suicide. The risk of suicidal behavior increases if there is a history of suicide attempts, exposure to adverse psychosocial circumstances, a family history of suicidal behavior, or comorbid psychotic disorders. Youths with depressive disorders are also at high probability of suicide attempts and suicide ideation and attempt rates increase with the number of life stressors. The suicide risk is greater for children with nonmelancholic depression (e.g., irritable mood).
risk of substance abuse, impaired family and peer relationships, early pregnancy, legal problems, educational and occupational underachievement, and poor adjustment to life stressors, including physical illness.

Children with DMDD have displayed elevated rates of social impairments, school suspension, and service use. Irritability in adolescence has predicted the development of major depressive and dysthymic disorders and generalized anxiety disorder (but not bipolar disorder) 20 yr later, as well as lower educational attainment and income.

**ETIOLOGY AND RISK FACTORS**

Current models of vulnerability to depressive disorders are grounded in gene by environment pathways. Genetic studies have repeatedly demonstrated the heritability of depressive disorders, with monozygotic twin studies finding concordance rates of 40–65%. In families, both bottom-up (children to parents) and top-down (parents to children) studies have shown a 2–4-fold bidirectional increase in depression among 1st-degree relatives. The exact nature of genetic expression remains unclear. Cerebral variations in structure and function (particularly serotoninergic), the function of the hypothalamic–pituitary–adrenal axis, difficult temperament/personality (i.e., negative affectivity), and ruminative, self-devaluing cognitive style have been implicated as components of biologic vulnerability. The great majority of depressive disorders arise in youth with long-standing psychosocial difficulties, among the most predictive of which are physical/sexual abuse, neglect, chronic illness, school difficulties (bullying, academic failure), social isolation, family or marital disharmony, divorce/separation, parental psychopathology, and domestic violence. Longitudinal studies demonstrate the greater importance of environmental influences in children who become depressed compared to adults who become depressed. Factors shown to be protective against the development of depression include a positive relationship with a parent, better family function, closer parental supervision/monitoring/involvement, a prosocial peer group, higher IQ, and greater educational aspirations.

**PREVENTION**

Numerous experimental trials have sought to demonstrate the effectiveness of psychological or educational strategies in preventing the onset of depressive disorders in children and adolescents. These programs generally have provided information about the link between depressed mood and depressogenic thoughts and behaviors, and training in skills intended to modify these thoughts and behaviors. A metaanalytic review found small to moderate effects of these programs at both postintervention and follow-up (overall mean effect size: 0.16), with selective programs (targeted at high-risk groups) performing better than universal programs. A Cochrane review found some evidence that depression prevention programs may have a small favorable effect compared with no intervention, but no effect compared to attention controls.

**SCREENING/CASE FINDING**

Adolescents presenting in the primary care setting should be queried, along with their parent(s), about depressed mood as part of the routine clinical interview. A typical screening question would be “Everyone feels sad or angry some of the time, how about you (or your teen)?” The parents of younger children can be queried about overt signs of depression, such as tearfulness, irritability, boredom, or social isolation. A number of standardized broadband screening instruments widely used in the primary care setting (e.g., Pediatric Symptom Checklist, Strengths and Difficulties Questionnaire, Vanderbilt ADHD Diagnostic Rating Scales) have items specific to sad mood, and as such can be used to focus the interview.

The role of universal depression screening using standardized narrowband (depression-specific) instruments is unclear. A Cochrane review found that the use of depression screening in primary care has little or no impact on the recognition, management, or outcome of depression. The United States Preventive Services Task Force recommends the use of depression screening instruments only among adolescents, and only when systems are in place to ensure adequate follow-up. Targeted screening of known high-risk groups (e.g., youth who are homeless, refugees, attracted to the same sex, involved with child welfare or juvenile justice) or of youth experiencing known psychosocial adversities (see “Etiology/Risk Factors” above) or self-reporting a dysphoric mood may be a higher-yield case-finding strategy than universal screening (Fig. 26-1).

**STEPPEd MANAGEMENT**

Because of the high rates of response to placebo and attention comparators as well as to brief therapy in the treatment of pediatric depression, clinical practice guidelines increasingly are advocating a stepped approach to the management of depressed youth. The stepped approach involves active case finding and initial management in the primary care setting if appropriate, with referral to increasingly intensive and specialized interventions as indicated by the clinical status of the patient.

**EARLY INTERVENTION**

Youth and/or their parents presenting in the primary care setting who self-report, or respond affirmatively to queries about, a distressing life experience or a depressed or irritable mood, should be offered the opportunity to talk about the situation with the pediatric practitioner (in private with the older youth as indicated). By engaging in active listening (e.g., “I hear how upset you have been feeling, tell me more about what happened to make you feel that way”), the pediatric practitioner can begin to assess the onset, duration, context, and severity of the symptoms, and associated dangerousness, distress, and functional impairment. In the absence of acute dangerousness (e.g., suicidality, psychosis, substance abuse) and significant distress or functional impairment, the pediatric practitioner can schedule a follow-up appointment within 1-2 wk to conduct a depression assessment. At this follow-up visit, to assist with decision making around appropriate level of care, a depression screening instrument can be administered (Table 26-4) and additional risk factors (see "Etiology/Risk Factors" above) can be explored.

For mild symptoms (manageable and not functionally impairing) and in the absence of major risk factors (e.g., suicidality, psychosis, substance use, history of depression, mania, or traumatic exposures, parental psychopathology [particularly depression]) or severe family dysfunction), guided self-help (anticipatory guidance) with watchful waiting may suffice. Guided self-help can include provision of educational materials (e.g., pamphlets, books, workbooks, internet sites) that provide information to the youth about dealing with stressful situations; and advice to parents about strengthening the parent-child relationship and modifying adverse environmental exposures (e.g., taking action against bullying, increasing opportunities for social interaction/support, protecting the child from exposure to marital discord) as depressogenic buffers. During the period of guided self-help, additional follow-up visits should be scheduled.

For youth who continue to have mild depression after a few weeks of guided self-help, supportive therapy by a mental health professional (ideally colocated in the primary care, school, or community setting) may be an appropriate subsequent step. Supportive psychotherapy, which can be delivered in individual or group formats, focuses on teaching thoughts (e.g., positive self-talk) and behaviors (e.g., pleasurable activities, relaxation, problem-solving, effective communication) known to ameliorate depressive symptoms, as well as providing concrete social or material problem-solving assistance to the youth or family as needed.

**TREATMENT**

For youth who have not responded to approximately 4-8 wk of supportive psychotherapy, or who from the outset exhibit moderate to severe, comorbid, or recurrent depression or suicidality, or who have a history of mania, traumatic exposures or severe family dysfunction or psychopathology, assessment and treatment in the specialty mental health setting by a child-trained mental health clinician should be provided (see Chapter 20). The mental health clinician should be
Modest (0.35 and 0.26, respectively). CBT focuses on identifying and correcting cognitive distortions that may lead to depressed mood and teaches problem-solving, behavior activation, social communication, and emotional regulation skills to combat depression. Interpersonal therapy focuses on enhancing interpersonal problem solving and social communication to decrease interpersonal conflicts. Each of these therapies typically involves approximately 8-12 weekly visits.

Limited evidence suggests that family therapy may be more effective than no treatment on decreasing depression and improving family functioning. Because of the heterogeneity of the evidence base, however, the use of better supported therapies would at this time seem to be preferable over family therapy.

Two selective serotonin reuptake inhibitors (SSRIs), fluoxetine and escitalopram, are the only antidepressants approved by the FDA trained to the appropriate level of competence in the specific services he/she is asked to provide.

For moderate to severe depression, specific manualized psychotherapies, antidepressant medication, or a combination of the two should be provided. At present, there is insufficient evidence upon which to base definitive conclusions about the relative effectiveness of these treatments. The main goal of the acute treatment phase is to achieve response, which typically is defined as at least a 50% reduction in depressive symptoms as assessed by a standardized rating scale (see Table 26-4). Full recovery (i.e., absence of a depressive diagnosis) should be the ultimate treatment goal.

Clinical trials of acute treatments have generated support for the efficacy of cognitive-behavioral therapy (CBT) and interpersonal therapy as monotherapies in depressed youth, but effect sizes are

Figure 26-1 Detection of depression in adolescents in nonspecialist settings. *If patient scores < 2, generally no further action is needed. (From Thapar A, Collishaw S, Pine DS, Thapar AK: Depression in adolescence. Lancet 379:1056–1066, 2012. Fig. 1.)
for the treatment of depression, and fluoxetine alone is approved for preadolescents (see Chapter 21.1). These agents should be 1st-line for pharmacotherapy of pediatric depression, unless other factors (e.g., comorbidities, side-effect profiles, personal or family history of response to a specific medication) favor an alternative SSRI (preferably sertraline or citalopram). Resource limitations may necessitate provision of pharmacotherapy in the primary care setting; the safety and efficacy of this practice can be enhanced by regular consultation with a child and adolescent psychiatrist.

**Randomized controlled trials (RCTs)** of the effectiveness of antidepressants are mixed. Based on a large meta-analysis of RCTs, approximately 60% of youths with depression respond to antidepressants (vs. 50% for placebo), yielding a *number needed to treat* of 10, but only around 30% of medicated depressed youth experience symptom remission. Fluoxetine has consistently demonstrated greater efficacy, with a number needed to treat of 6, and is the only SSRI separating from placebo in studies of depressed preadolescents. Studies of other classes of antidepressant medications have not demonstrated clear superiority over placebo, and tricyclic medications and paroxetine in particular are not currently recommended for use in youth because of their clearly unfavorable risk:benefit profiles. The absolute risk for suicidal thoughts in youth with major depression approximates 3% (treated with antidepressant) versus 2% (given placebo), translating to a *number needed to harm* of 112.

Clinical severity, comorbidity, family conflict, low drug concentration, nonadherence, anhedonia, sleep difficulties, subsyndromal manic symptoms, and child maltreatment have all been related to treatment resistance. Approximately 50% of depressed youth failing to respond to the first SSRI respond after switching to a second antidepressant medication plus CBT, versus approximately 40% who respond to a second medication alone. For youth with psychotic depression, augmentation of the antidepressant with an atypical antipsychotic medication should be considered, while monitoring closely for side effects.

The SSRIs have been well tolerated by children and adolescents. The most common side effects include irritability, gastrointestinal symptoms, sleep disturbance, restlessness, diaphoresis, headaches, changes in appetite, dizziness, dry mouth, and sexual dysfunction. Approximately 5% of youths, particularly children, develop increased impulsivity, agitation, and irritability (behavioral activation) on SSRIs, but the symptoms quickly resolve when the medication dose is reduced or the medication is discontinued. More rarely, the use of antidepressants has been associated with serotonin toxicity, increased predisposition to bleeding, abnormal heart rhythms (citalopram causes dose-dependent QT-interval prolongation and should not be prescribed at doses greater than 40 mg/day) and increased suicidal thoughts.

The initial dose of SSRI medication should be approximately one-half of the adult dose (e.g., 10 mg of fluoxetine). Some studies have reported that the half-lives of SSRIs other than fluoxetine are much shorter in children than in adults; therefore daily withdrawal side effects can be observed with these medications if they are administered once daily. Clinical response, tolerability, and emergence of behavioral activation, mania, or suicidal thoughts should be assessed frequently (preferably weekly) for the first 4 wk. If the youth has safely tolerated the antidepressant, the initial dose may be doubled at 4 wk if an adequate response (at least 50% reduction in symptom severity as measured by standardized rating scales) has not been achieved, with biweekly monitoring recommended. Patients who have responded by 8 wk can then be monitored less frequently (up to monthly) until remission (no longer meets diagnostic criteria) has been achieved. Patients treated in the primary care setting who have not responded by 8 wk or remitted by 12 wk should be referred to the specialty mental health setting for advanced care.

Because of the high rate of recurrence, successful treatment should continue for 6-12 mo. At the conclusion of treatment, all antidepressants should be discontinued gradually to avoid withdrawal symptoms (gastrointestinal upset, disequilibrium, sleep disruption, flu-like symptoms, sensory disturbances). Patients with recurrent (2 or more), chronic, or severe major depression can require treatment beyond 12 mo.

Table 26-5 summarizes screening, assessment, and treatment recommendations for depression.

### Table 26-4: Depression-Specific Screening Instruments

<table>
<thead>
<tr>
<th>NAME OF INSTRUMENT</th>
<th>INFORMANT(S)</th>
<th>AGE RANGE</th>
<th>NUMBER OF ITEMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preschool Feelings Checklist</td>
<td>Parent</td>
<td>3-5.6 yr</td>
<td>20</td>
</tr>
<tr>
<td>Preschool Symptom</td>
<td>Self-Report Youth, Parent, Teacher</td>
<td>3-5 yr</td>
<td>25</td>
</tr>
<tr>
<td>Center for Epidemiologic Studies-Depression-Children</td>
<td>Youth</td>
<td>6-18 yr</td>
<td>20</td>
</tr>
<tr>
<td>Children’s Depression Rating Scale-Revised</td>
<td>Youth, Parent, Clinician</td>
<td>6-18 yr</td>
<td>47</td>
</tr>
<tr>
<td>Children’s Depression Inventory-Second Edition</td>
<td>Youth, Parent, Teacher</td>
<td>7-17 yr</td>
<td>28/17/12</td>
</tr>
<tr>
<td>Depression Self-Rating Scale</td>
<td>Youth</td>
<td>7-13 yr</td>
<td>18</td>
</tr>
<tr>
<td>Beck Depression Inventory for Youth</td>
<td>Youth</td>
<td>7-14 yr</td>
<td>20</td>
</tr>
<tr>
<td>Mood and Feelings Questionnaire</td>
<td>Youth, Parent</td>
<td>7-18 yr</td>
<td>33-34</td>
</tr>
<tr>
<td>Reynolds Child Depression Scale</td>
<td>Youth</td>
<td>8-13 yr</td>
<td>30</td>
</tr>
<tr>
<td>Reynolds Adolescent Depression Scale-Second Edition</td>
<td>Youth</td>
<td>11-20 yr</td>
<td>30</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>Youth</td>
<td>13+ yr</td>
<td>21</td>
</tr>
<tr>
<td>Patient Health Questionnaire-9</td>
<td>Youth</td>
<td>13-17 yr</td>
<td>9</td>
</tr>
</tbody>
</table>

**Bibliography is available at Expert Consult.**
Bibliography


26.2 Bipolar and Related Disorders
Heather J. Walter, Natalija Bogdanovic, and David R. DeMaso

DESCRIPTION
The bipolar and related disorders include bipolar I, bipolar II, cyclothymic, and other specified/ unspecified bipolar and related disorders, as well as bipolar and related disorder caused by another medical condition.

A manic episode (Table 26-6) is characterized by a distinct period of at least 1 wk in which there is an abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy that is present for most of the day, nearly every day (or any duration if hospitalization is necessary). The episode is associated with characteristic cognitive and behavioral symptoms, including disturbances in self-regard, speech, attention, thought, activity, impulsivity, and sleep. To diagnose bipolar I disorder, criteria must be met for at least 1 manic episode, and the episode must not be better explained by a psychotic disorder. The manic episode may have been preceded by and may be followed by hypomanic or major depressive episodes. Bipolar I disorder is rated as mild, moderate, or severe in the same way as the depressive disorders (see Description section of Chapter 26.1).

To diagnose bipolar II disorder, criteria must be met for at least 1 hypomanic episode and at least 1 major depressive episode. A hypomanic episode is similar to a manic episode, but is briefer (at least 4 days) and less severe (causes less impairment in functioning, is not associated with psychosis, and would not require hospitalization). In bipolar II disorder, there must never have been a manic disorder, the episodes must not be better explained by a psychotic disorder, and the symptoms of depression or the unpredictability caused by frequent alternation between periods of depression and hypomania must cause clinically significant distress or functional impairment. Bipolar II disorder is rated as mild, moderate, or severe in the same way as bipolar I disorder.

Cyclothymic disorder is characterized by a period of at least 1 yr (in children and adolescents) in which there are numerous periods with hypomanic and depressive symptoms that do not meet criteria for a hypomanic episode or a major depressive episode, respectively.

Other specified/unspecified bipolar and related disorders (subsyndromal bipolar disorder) applies to presentations in which symptoms characteristic of a bipolar and related disorder are present and cause distress or functional impairment, but do not meet the full criteria for any of the disorders in this diagnostic class. Although this diagnosis (formerly known as bipolar disorder, not otherwise specified)

Table 26-5
Screening and Treatment for Major Depressive Disorder in Youths

<table>
<thead>
<tr>
<th>RECOMMENDATION</th>
<th>ADOLESCENTS (12-18 Yr)</th>
<th>CHILDREN (7-11 Yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening</strong></td>
<td>Screen (when systems for diagnosis, treatment, and follow-up are in place) Grade B</td>
<td>No recommendations Grade I (insufficient evidence)</td>
</tr>
<tr>
<td><strong>Risk assessment</strong></td>
<td>Risk factors for major depressive disorder include parental depression, having comorbid mental health or chronic medical conditions, and having experienced a major negative life event</td>
<td></td>
</tr>
<tr>
<td><strong>Screening tests</strong></td>
<td>The following have been shown to do well in teens in primary care settings: Patient Health Questionnaire for Adolescents (PHQ-A) Beck Depression Inventory—Primary Care version (BDI-PC)</td>
<td>Screening instruments perform less well in younger children</td>
</tr>
<tr>
<td><strong>Treatments</strong></td>
<td>Among pharmacotherapies, fluoxetine, a SSRI, has been found efficacious. However, because of risk of suicidality, SSRIs should be considered only if clinical monitoring is possible. Various modes of psychotherapy, and pharmacotherapy combined with psychotherapy, have been found efficacious</td>
<td>Evidence on the balance of benefits and harms of treatment of younger children is insufficient for a recommendation</td>
</tr>
</tbody>
</table>

For a summary of the evidence systematically reviewed in making these recommendations, the full recommendation statement, and supporting documents, please go to http://www.AHRQ.gov/clinic/USPSTF/USPSCHDEPR.htm.

Table 26-6
DSM-5 Diagnostic Criteria for a Manic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 wk and present most of the day, nearly every day (or any duration if hospitalization is necessary).

B. During the period of mood disturbance and increased energy or activity, 3 (or more) of the following symptoms (4 if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:
   1. Inflated self-esteem or grandiosity.
   2. Decreased need for sleep (e.g., feels rested after only 3 hr of sleep).
   3. More talkative than usual or pressure to keep talking.
   4. Flight of ideas or subjective experience that thoughts are racing.
   5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
   6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity).
   7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

D. The episode is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication, other treatment) or to another medical condition.

Note: A full manic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiologic effect of that treatment is sufficient evidence for a manic episode and, therefore, a bipolar I diagnosis.

Note: Criteria A-D constitute a manic episode. At least 1 lifetime manic episode is required for the diagnosis of bipolar I disorder.

heretofore had frequently been applied to children with severe and chronic mood and behavioral dysregulation who did not precisely fit other diagnostic categories, the empiric support for the validity of this practice has been sparse. Many children who formerly received this diagnosis will meet criteria for DMDD (see Chapter 26.1).

In adolescents, the clinical manifestations of bipolar disorder are similar to those in adults, and psychosis (delusions, hallucinations) often is an associated symptom. Mood in a manic episode is often described as euphoric, excessively cheerful, high, or “feeling on top of the world.” During the episode, the adolescent may engage in multiple new projects that are initiated with little knowledge of the topic and often at unusual hours (in the middle of the night). Inflated self-esteem is usually present, ranging from uncomplicated self-confidence to marked grandiosity, and may reach delusional proportions. The adolescent may sleep little if at all for days at a time and nonetheless feel rested and full of energy. Speech can be rapid, pressured, and loud and characterized by jokes, puns, amusing irrelevancies, and theatricality. Frequently there is a flight of ideas evidenced by a nearly continuous flow of accelerated speech, with abrupt shifts from one topic to another. Distractibility is evidenced by an inability to censor irrelevant extraneous stimuli, which often prevents an individual with mania from engaging in a rational conversation. The expansive mood, grandiosity, and poor judgment often lead to reckless involvement in activities with high potential for personal harm.

There is controversy about the applicability of the bipolar diagnostic criteria to prepubertal children. It may be developmentally normal for children to be elated, expansive, grandiose, or talkative, reducing the specificity of these symptoms to this disorder. In addition, the distractibility, overactivity, and impulsivity formerly ascribed to bipolar disorder by some investigators may be better explained by a diagnosis of ADHD. The presentations of severe irritability formerly diagnosed as bipolar disorder may be better captured by the diagnosis of DMDD.

Epidemiology
The lifetime prevalence of the bipolar disorders among adults approximates 1-3%; rates among youth generally have been less than 1%. For bipolar I, the male:female ratio approximates 1.1:1.

Clinical Course
The mean age of onset of the first manic episode is approximately 18 yr for bipolar I disorder. Premorbid problems are common in bipolar disorder, especially difficulties with mood and behavioral regulation. Premorbid anxiety also is common. The early course of adolescent-onset bipolar disorder appears to be more chronic and refractory to treatment than adult-onset bipolar disorder. Comorbidity predicts functional impairment and age at onset predicts duration of episodes. Sleep impairment and family conflict are inversely related to favorable treatment response, suggesting important targets for treatment. The bipolar disorders are highly recurrent, and more than 80% of bipolar I patients go on to have additional mood episodes. Recurrent episodes can approximate 4 in 10 yr, with the interepisode interval shortening as the patient ages. Although the majority of patients with bipolar I return to a fully functional level between episodes, approximately one-third continue to be symptomatic and functionally impaired between episodes. In a 14 yr follow-up study, children 4-16 yr of age exceeding the clinical cutpoint for the dysregulation (“bipolar”) profile on the Child Behavior Checklist were found to have increased rates of anxiety, mood, disruptive behavior, and substance abuse disorders in adulthood.

Differential Diagnosis
A number of psychiatric disorders, general medical conditions, and medications can generate manic-like symptoms and must be distinguished from the bipolar and related disorders. The psychiatric disorders include ADHD, oppositional defiant, intermittent explosive, posttraumatic stress, depressive, anxiety, substance abuse, and borderline personality disorders. Medical conditions include neurologic disorders, endocrine disorders, infectious diseases, tumors, anemia, uremia, and vitamin deficiencies. Medications include androgens, bronchodilators, cardiovascular medications, corticosteroids, chemo-

Therapy agents, thyroid preparations, and certain psychiatric medications (benzodiazepines, antidepressants, stimulants). The diagnosis of a bipolar disorder should be made after these other explanations for the observed symptoms have been ruled out.

Comorbidity
Nearly 75% of individuals with bipolar disorders have co-occurring anxiety disorders, and nearly 50% have co-occurring attention, disruptive/impulse control/conduct, and substance use disorders.

Sequela
The lifetime risk of suicide in individuals with bipolar disorder is estimated to be at least 15 times that of the general population. Youths with bipolar disorders are also at high risk for substance abuse, antisocial behavior, impaired academic performance, impaired family and peer relationships, and poor adjustment to life stressors.

Etiology/Risk Factors
Twin studies suggest the heritability of bipolar disorder is greater than 60%. Offspring of parents with bipolar disorders are at high risk for early-onset bipolar disorders, and there is an average 10-fold increased risk among adult relatives of individuals with bipolar disorder, with the magnitude of risk increasing with the degree of kinship. Bipolar disorder and schizophrenia likely share a genetic origin, reflected in familial co-aggregation of the two disorders.

Dysthymic (sad), cyclothymic (labile), or hyperthymic (irritable) temperaments may prestage eventual bipolar disorder. Premorbid anxiety and dysphoria also are common, and approximately 20% of youth with major depression go on to experience manic episodes by adulthood. Similar to findings in adults, factors that predict the eventual development of mania in depressed youth include a depressive episode characterized by rapid onset, psychomotor retardation, and psychotic features, a family history of affective disorders, especially bipolar disorder, and a history of mania or hypomania after treatment with antidepressants.

Prevention
Although empiric support is sparse, 1 randomized controlled study demonstrated the effectiveness of family-focused treatment versus an educational control in hastening and sustaining recovery from mood symptoms in a high familial risk cohort of youth with subsyndromal symptoms of mania. Family-focused treatment is a manualized psychoeducational intervention designed to reduce family stress, conflict, and affective arousal by enhancing communication and problem-solving between youth and their caregivers. Pharmacologic interventions for subsyndromal mania have produced equivocal results.

Case Finding
Cardinal manic symptoms of elation and grandiosity occurring in adolescents as a discrete episode should alert pediatric practitioners to the possibility of a bipolar or related disorder. Because of the complexity of these disorders, any suspected cases should be referred to the specialty mental health setting for comprehensive assessment (see Chapter 20) and treatment (see Chapter 21).

Treatment
For mania in bipolar I disorder, medication is the primary treatment. Among traditional mood stabilizer medications (lithium carbonate, divalproex sodium, carbamazepine), only lithium is approved by the FDA for the treatment of bipolar disorder from age 12 yr (see Chapter 21.1). At present lithium has only open-label empirical support, with an overall response rate approximating 40%. There is no RCT evidence supporting the efficacy of divalproex sodium or carbamazepine. No other anticonvulsant medications sometimes used for the treatment of mania (oxcarbazepine, lamotrigine, topiramate) have FDA approval or RCT evidence of efficacy. In contrast, atypical antipsychotic medications (e.g., quetiapine, aripiprazole, ziprasidone, risperidone, olanzapine) have an overall 66% response with significant separation from placebo/active comparator in RCTs, and as such are considered to be
1st-line treatments for mania. The FDA has approved aripiprazole, risperidone, and quetiapine for the treatment of bipolar disorder from age 10 yr, and olanzapine from age 13 yr (see Chapter 21.1). The choice of antipsychotic medication is based upon factors such as side-effect profiles, adherence considerations, and a positive response of a family member.

Medication trials should be systematic, and the duration of trials should be sufficient (generally 6–8 wk) to determine the agent’s effectiveness. Care should be taken to avoid unnecessary polypharmacy, in part by discontinuing agents that have not demonstrated significant benefit. Because all of these medications are associated with significant side effects, careful monitoring of baseline and follow-up indices is imperative. Side effects of lithium include reduced urine concentrating ability, hypothyroidism, hyperparathyroidism, weight gain, and renal failure. Acute overdose (level > 1.5 mEq/L) manifests with neurologic symptoms (tremor, ataxia, nystagmus, hyperreflexia, myoclonus, slurred speech, delirium, coma, seizures), and altered renal function. Toxicity is enhanced when dehydrated or with drugs that affect renal function (nonsteroidal antiinflammatory drugs, angiotensin-converting enzyme inhibition) Neuroleptic malignant syndrome has been reported in patients also taking antipsychotic drugs. Atypical antipsychotics cause weight gain, metabolic aberrations (diabetes, hyperlipidemia), and cardiac effects. Withdrawal of medication has been associated with increased risk of relapse.

The regimen needed to stabilize acute mania should be maintained for 12–24 mo. Maintenance therapy is often needed for adolescents with bipolar I disorder, and some patients need lifelong medication. Any attempts to discontinue prophylactic medication should be done gradually, while closely monitoring the patient for relapse.

For depression in bipolar II disorder, antidepressant medication may be used once a mood-stabilizing medication has been initiated. Lamotrigine as adjunctive or monotherapy also may be helpful for adolescents with bipolar depression. Comorbid ADHD can be treated with stimulant medication once a mood-stabilizing medication has been initiated.

Psychotherapy is a potentially important adjunctive treatment for the bipolar disorders. However, a Cochrane review of 7 RCTs of family interventions found only heterogeneous evidence of effectiveness, precluding definitive conclusions about their use. Factors known to adversely influence response to therapy include high-conflict families and sleep impairment, suggesting the importance of targeting these factors in treatment.

**LEVEL OF CARE**

Most youths with bipolar disorders can be safely and effectively treated as outpatients, provided that an appropriate schedule of visits and laboratory monitoring can be maintained through the course of treatment. Youths who are suicidal or psychotic typically require inpatient care.

*Bibliography is available at Expert Consult.*
Bibliography

Youth suicide is a major and tragic public health problem. For youth between the ages of 15 and 24 yr in the United States, suicide is the 3rd leading cause of death, with approximately 4,600 lives lost each year. Globally, suicide rates for youth ages 15-19 yr are 7.4/100,000 persons, the 4th leading cause of death for males and the 3rd for females. There are a number of psychiatric, social, cultural, and environmental risk factors for suicidal behavior, and knowledge of these risk factors can facilitate identification of youths at highest risk (Fig. 27-1).

**Epidemiology**

**Suicidal Ideation and Attempts**

Based on the 2011 Youth Risk Behavior Survey, almost one-third of 9th through 12th grade students nationwide in the United States felt so sad or hopeless almost every day for 2 or more wk in a row during the previous year that they stopped doing some usual activities. During that same time period, nearly 16% of the students reported that they had seriously considered attempting suicide and 8% reported that they had actually attempted suicide. A suicide attempt in the previous year that resulted in an injury, poisoning, or overdose that had to be treated by a doctor or nurse was reported by more than 2% of students.

It is estimated that for every completed youth suicide, as many as 200 suicide attempts are made. Ingestion of medication is the most common method of attempted suicide. The 15-19 yr old age group is the most likely to intentionally harm themselves by ingestion, receive treatment in emergency departments, and survive. Attempts are more common in adolescent females than males (approximately 4:1), and in Hispanic females compared to their non-Hispanic counterparts. Gay, lesbian, bisexual, and transgender youths also have disproportionately high rates of suicide attempts. Attempters who have made prior suicide attempts, who used a method other than ingestion, and who still want to die are at increased risk for completed suicide.

**Suicide Completions**

In the United States, completed suicide is very rare before puberty. Rates of completed suicide increase steadily across adolescence into young adulthood, peaking in the early 20s. In the past 60 yr, the suicide rate has quadrupled among 15-24 year old males and has doubled for females of the same age. The male:female ratio for completed suicide rises with age from 3:1 in children to approximately 4:1 in 15-24 yr olds, and to greater than 6:1 among 20-24 yr olds.

Native Americans/Alaska Natives have highest rates of completed suicide of all ethnic groups, with nearly 21 deaths per 100,000. White youth are the next highest at almost 12 deaths per 100,000. The ethnic groups with the lowest risk are African-Americans, Hispanics, Asians, and Pacific Islanders. Over time the suicide rate among African-American, Hispanic, and other minority males has increased, while the rate among white males has remained steady.

Access to means has been linked to suicide rates among different groups in the population and different geographical areas of the world (Fig. 27-2). Firearms are the most common method used to complete suicide in the United States, and account for 56% of male suicides and 30% of female suicides. In females, poisonous ingestions, especially overdoses of medications, are the most common method used to complete suicide, and account for 37% of female suicides, compared to only 12% of male suicides. Hanging is the third most common method used to complete suicide and accounts for 25% of male and female suicides. Firearms are the most lethal method of suicide completion; the death rate with respect to firearms is approximately 80-90%, whereas the death rate is only 1.5-4% for overdoses.

**Risk Factors**

In addition to age, race/ethnicity, and a history of a previous suicide attempt, there are multiple risk factors that predispose youths to suicide (Table 27-1).

**Preexisting Mental Disorder**

Approximately 90% of youths who complete suicide have a preexisting psychiatric illness, most commonly major depression (see Chapter 26.1). Among females, chronic anxiety, especially panic disorder, also is associated with suicide attempts and completion (see Chapter 25).
Among males, conduct disorder and substance use convey increased risk. Comorbidity of a substance use disorder (see Chapter 114), a depressive disorder (see Chapter 26.1), and conduct disorder (see Chapter 29.1) are linked to suicide by firearm. Schizophrenia spectrum disorders (see Chapter 31) are linked to suicide attempts and completions.

### Cognitive Distortions

Negative self-attributions can contribute to the hopelessness that is commonly associated with suicidality; hopelessness may contribute to approximately 55% of the explained variance in continued suicidal ideation. Many youth who are suicidal hold negative views of their own competence, have poor self-esteem, and have difficulty identifying sources of support or reasons to live. Many youngsters lack the coping strategies necessary to manage strong emotions and instead tend to catastrophize and engage in all-or-nothing thinking.

### Biologic Factors

Postmortem studies show that there are observable differences between the brains of individuals who have completed suicide and those who died from other causes. The brain systems that may be related to suicide completion are the serotonergic system, adrenergic system, and the hypothalamic–pituitary axis. Family history of mental disorders also is linked to completed suicide.

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**Figure 27-1** Key risk factors for adolescent self-harm and suicide. (From Hawton K, Saunders KEA, O’Connor RC: Self-harm and suicide in adolescents. Lancet 379:2373–2380, 2012, Fig. 2.)


*Per 100,000 population.

**Table 27-1** Risk Factors for Self-Harm and Suicide in Adolescents

<table>
<thead>
<tr>
<th>SOCIODEMOGRAPHIC AND EDUCATIONAL FACTORS</th>
<th>INDIVIDUAL NEGATIVE LIFE EVENTS AND FAMILY ADVERSITY</th>
<th>PSYCHIATRIC AND PSYCHOLOGICAL FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female for self-harm and male for suicide)—most countries*</td>
<td>Low socioeconomic status*</td>
<td>Mental disorder,* especially depression, anxiety, attention deficit hyperactivity disorder</td>
</tr>
<tr>
<td>Low socioeconomic status*</td>
<td>Lesbian, gay, bisexual, or transgender sexual orientation</td>
<td>Drug and alcohol misuse*</td>
</tr>
<tr>
<td>Lesbian, gay, bisexual, or transgender sexual orientation</td>
<td>Restricted educational achievement*</td>
<td>Impulsivity</td>
</tr>
<tr>
<td>Restricted educational achievement*</td>
<td>Adverse childhood experiences*</td>
<td>Low self-esteem</td>
</tr>
<tr>
<td>Parental separation or divorce*</td>
<td>History of physical or sexual abuse</td>
<td>Poor social problem-solving</td>
</tr>
<tr>
<td>Parental death*</td>
<td>Parental mental disorder*</td>
<td>Perfectionism</td>
</tr>
<tr>
<td>Adverse childhood experiences*</td>
<td>Family history of suicidal behavior*</td>
<td>Hopelessness*</td>
</tr>
<tr>
<td>History of physical or sexual abuse</td>
<td>Marital or family discord</td>
<td>All the factors in the panel have been shown to be related to self-harm.</td>
</tr>
<tr>
<td>Parental mental disorder*</td>
<td>Bullying</td>
<td>*Shown to be related to suicide.</td>
</tr>
</tbody>
</table>

**Social, Environmental, and Cultural Factors**

Of youths who attempt suicide, 65% can name a precipitating event for their action. Most adolescent suicide attempts are precipitated by stressful life events (e.g., academic or social problems, being bullied, trouble with the law, family instability, questioning one’s sexual orientation, a newly diagnosed medical condition, or a recent or anticipated loss).

Suicide attempts may also be precipitated by exposure to news of another person’s suicide or by reading about or viewing a suicide portrayed in a romantic light in the media. Media coverage of suicide is linked to fluctuating incidence rates of suicides, particularly among adolescents. Glorification or sensationalization of suicide in the media has found to be associated with an increase in suicides. When media coverage includes a detailed description of specific means used, the use of that particular method may increase in the overall population.
For some immigrants, suicidal ideation can be associated with high levels of acculturative stress, especially in the context of family separation and limited access to supportive resources. Physical and sexual abuse can also increase one's risk of suicide with 15-20% of female suicide attempters having had a history of abuse. There is a general association between family conflict and suicide attempts; this association is strongest in children and early adolescents. Family psychopathology and a family history of suicidal behavior convey excess risk. The lack of supportive social relations with peers, parents, and school personnel have an interactive relationship in increasing the risk of suicide among youth.

**Protective Factors**

Protective factors can provide a counterbalance for those contemplating suicide. They may include a sense of family responsibility, life satisfaction, social support, coping and problem-solving skills, religious faith, intact reality testing, and solid therapeutic relationships (e.g., pediatrician, teacher, therapist).

### ASSESSMENT AND INTERVENTION

Pediatric practitioners should consider suicide potential and the need for mental health assessment in the context of adverse information elicited in child/parent psychosocial histories (e.g., HEADSS Psycho-social Risk Assessment; see Table 20-2 in Chapter 20), screening measure scores out of the normal range (e.g., Pediatric Symptom Checklist), or self-reported statements or behaviors from patients and/or parents.

All suicidal ideation and attempts should be taken seriously and require a thorough assessment by a child-trained mental health clinician to evaluate the youth’s current state of mind, underlying psychiatric conditions, and ongoing risk of harm. Emergency mental health assessment is needed for immediate threat to self (i.e., suicidal intent and plan); urgent mental health assessment (48-72 hr) is needed for severe psychiatric symptoms, significant change in overall functioning, and/or suicidal ideation without intent or plan. Routine mental health assessment is appropriate for mild to moderate psychiatric symptoms without suicidal ideation.

Pediatric practitioners should expect the mental health clinician to evaluate the presence and degree of suicidality and underlying risk factors. The reliability and validity of child interviewing is affected by the child's level of cognitive development and well as their understanding of the relationship between their emotions and behavior. Confirmation of the youth's suicidal behavior can be obtained from information gathered by interviewing others who know the child or adolescent. It is not unusual for there to be a discrepancy between patient and parent reports, with both children and adolescents being more likely to disclose suicidal ideation and suicidal actions than their parents.

In the mental health assessment, suicidal ideation can be assessed by explicit questions posed in a nonjudgmental, noncondescending, matter-of-fact approach. The *Ask Suicide-Screening Questionnaire* is a validated 4-item measure that has been shown in the emergency room setting to have high sensitivity and negative predictive value in identifying youth at risk for suicide ideation and behavior: (1) *In the past few weeks, have you felt that you or your family would be better off if you were dead?* (2) *In the past few weeks, have you wished you were dead?* (3) *In the past weeks, have you been having thoughts about killing yourself?* (4) *Have you ever tried to kill yourself?*

The assessment of a suicidal attempt should include a detailed exploration of the hours immediately preceding the attempt to identify precipitants as well as the circumstances of the attempt itself so as to fully understand the patient's intent and potential lethality. The calculation of the level of suicide concern is complex requiring a determination across a spectrum of risk (Fig. 27-3). At the low end of the risk spectrum are youth with thoughts of death or wanting to die, but without suicidal thoughts, intent, or a plan. Those with highly specific suicide plans, preparatory acts or suicide rehearsals, and clearly articulated intent are at the high end. A suicidal history, presently impaired judgment (as seen in altered mental states including depression, mania, anxiety, intoxication, substance abuse, psychosis, trauma-reactive, hopelessness, rage, humiliation, impulsivity) as well as poor social support further exacerbates the heightened risk. Among adolescents who consider self-harm, those who carry out (enactors) self-injury are more likely to have family or friends (or think that their peers) engaged in self harm, and are more impulsive than those who only have thoughts of self-harm (ideators).

For youth who are an imminent danger to themselves, inpatient level of psychiatric care is necessary to ensure safety, clarify diagnoses, and comprehensively plan treatment. These patients can be hospitalized voluntarily or involuntarily. It is helpful for the pediatric practitioner to have an office protocol to follow in these situations. This protocol should take into consideration state laws regarding involuntary hospitalization, transportation options, nearest emergency assessment site, necessary forms for hospitalization, and available emergency mental health consultants.

For those youth suitable for treatment in the outpatient setting, an appointment should be scheduled within a few days with a mental health clinician. Ideally, this appointment should be scheduled before leaving the assessment venue, as nearly 50% of those who attempt suicide fail to follow through with the mental health referral. A procedure should be in place to contact the family if the family fails to complete the referral.

Through follow-up office visits, pediatric practitioners can help support and facilitate the implementation of psychotherapies (e.g., cognitive-behavioral therapy, dialectical behavioral therapy, interpersonal therapy, and/or family therapy) that target the specific psychiatric disorders and the emotional dysphoria or behavioral dysregulation that accompany suicidal ideation or behavior. In conjunction with a child and adolescent child psychiatrist, psychotropic medications may be used as indicated to treat underlying psychiatric disorders. Pediatric practitioners also can encourage social connectedness to peers and to community organizations (e.g., school or church), as well as promote help-seeking (e.g., talking to a trusted adult when distressed) and wellness (e.g., sleep, exercise, relaxation, nutrition) behaviors. In the unfortunate circumstance of a completed suicide, pediatricians can offer support to the family, particularly by monitoring for adverse bereavement responses in siblings and parents.

### PREVENTION

Suicide prevention is of high global importance. Yet, even in high-risk populations suicide is a comparatively rare event. Even the aforementioned risk factors associated with suicide are relatively common and individually not strong predictors of suicide. The assessment is complicated by patients that may attempt to conceal their suicide thoughts and by those who express suicidal thoughts without serious intent.

Suicide screening has been challenging because most screening instruments have variable sensitivity and specificity. In addition, the burden of follow-up mental health evaluations for those who screen positive has been daunting. Although primary care–feasible screening tools may be helpful to identify some adults at increased risk for suicide, they have, to date, demonstrated limited ability to detect suicide risk in adolescents.

Prevention strategies in the pediatric medical home include training staff to recognize and respond to the warning signs of suicide, screening for and treating depression, educating patients/parents about warning signs for suicide, and restricting access to modes of lethal self-harm. Youth have increased rates of suicide attempts and completions if they live in homes where firearms are present and available. When recommended by their primary care providers, most parents restrict access of their children to guns and medications. Pediatric practitioners should consider counseling parents to either remove firearms from the home entirely or securely lock guns and ammunition in separate locations. Anecdotal evidence suggests youth frequently know where guns and keys to gun cabinets are kept, even though parents may think they do not. The same recommendation applies to restricting access to potentially lethal prescription and nonprescription...
medications (e.g., containers of more than 25 acetaminophen tablets) and alcohol. These approaches emphasize the importance of restriction of access to means for suicide to prevent self-harm.

Screening for suicide in schools is also fraught with problems related to low specificity of the screening instrument and paucity of referral sites, as well as poor acceptability among school administrators. Gatekeeper (e.g., student support personnel) training appears effective in improving skills among school personnel and is highly acceptable to administrators but has not been shown to prevent suicide. School curricula (e.g., Signs of Suicide) have shown some preventive potential by teaching students to recognize the signs of depression and suicide in themselves and others, and to provide students with specific action steps necessary for responding to these signs. Peer helpers have not generally been shown to be efficacious.

Bibliography is available at Expert Consult.

Figure 27-3 Assessment and interventions with potentially suicidal patients. (Adapted from Suicide Prevention Resource Center, WICHE Center for Mental Health Program. Suicide prevention primer. Available at http://www.sprc.org/sites/sprc.org/files/primer.pdf.)
Bibliography
Eating disorders (EDs) are characterized by body dissatisfaction related to overvaluation of a thin body ideal associated with dysfunctional patterns of cognition and weight-control behaviors that result in significant biologic, psychological, and social complications. Although largely affecting white, adolescent girls, EDs also affect boys and cross all racial, ethnic, and cultural boundaries. Early intervention in EDs improves outcome.
Anorexia nervosa (AN) involves significant overestimation of body size and shape, with a relentless pursuit of thinness that typically combines excessive dieting and compulsive exercising in the restrictive subtype; in the binge-purge subtype, patients might intermittently overeat and then attempt to rid themselves of calories by vomiting or taking laxatives, still with a strong drive for thinness (Table 28-1).

Bulimia nervosa (BN) is characterized by episodes of eating large amounts of food in a brief period, followed by compensatory vomiting, laxative use, and exercise or fasting to rid the body of the effects of overeating in an effort to avoid obesity (Table 28-2).

Children and adolescents with EDs may not fulfill criteria for AN or BN in the new Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) but fall into a new subcategory of Atypical AN, or a new category of Avoidant Restrictive Food Intake Disorder (ARFID) (Table 28-3), that includes a group of conditions in which food intake is restricted or avoided due to adverse feeding or eating experiences or the sensory qualities of food, resulting in significant nutritional deficiencies and problems with social interactions. Binge eating disorder (BED), in which binge eating is not followed regularly by any compensatory behaviors (vomiting, laxatives) is a stand-alone category in DSM-5 but shares many features with obesity (see Chapter 47). ED-NOS, often called "disordered eating," can worsen into full syndrome EDs.

**DEFINITIONS**

Anorexia nervosa (AN) involves significant overestimation of body size and shape, with a relentless pursuit of thinness that typically combines excessive dieting and compulsive exercising in the restrictive subtype; in the binge-purge subtype, patients might intermittently overeat and then attempt to rid themselves of calories by vomiting or taking laxatives, still with a strong drive for thinness (Table 28-1).

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**EPIDEMIOLOGY**

The classic features of AN include a white, early to middle adolescent girl of above-average intelligence and socioeconomic status, who is a conflict-avoidant, risk-aversive, perfectionist struggling with disturbances of anxiety and/or mood. BN tends to emerge in later adolescence, sometimes evolving from AN, and is typified by impulsivity and features of borderline personality disorder that are associated with depression and mood swings. The 0.5-1% and 3-5% incidence rates among younger and older adolescent females for AN and BN, respectively, probably reflect ascertainment bias in sampling and underdiagnosis in cases not fitting the typical profile. The same may be true of the significant gender disparity, in which female patients account for approximately 90% of patients with diagnosed EDs. Ten percent or more of some adolescent female populations have ED-NOS.

No single factor causes the development of an ED; sociocultural studies indicate a complex interplay of culture, ethnicity, gender, peers, and family. The gender dimorphism is presumably related to females having a stronger relationship between body image and self-evaluation, as well as the influence of the Western culture's thin body ideal on the development of EDs. Race and ethnicity appear to moderate the
Behavioral problems often related to developmental processes of adolescence triggering the emergence of the ED, and perpetuating factors that cause an ED to persist. EDs often begin with dieting but gradually progress to unhealthy habits that lessen the negative impact of associated psychosocial problems to which the affected person is vulnerable because of premorbid biologic and psychologic characteristics, family interactions, and social climate. When persistent, the biologic effects of starvation and malnutrition (e.g., true loss of appetite, hypothermia, gastric atony, amenorrhea, sleep disturbance, fatigue, weakness, and depression) combined with the psychologic rewards of increased sense of mastery and reduced emotional reactivity, actually maintain and reward pathologic ED behaviors. This positive reinforcement of behaviors and consequences, generally viewed by parents and others as negative, helps to explain why affected persons characteristically deny that a problem exists and resist treatment. Although noxious, purging can be reinforcing owing to a reduction in anxiety triggered by overeating; purging also can result in short-term, but reinforcing, improvement in mood that is related to changes in neurotransmitters. In addition to an imbalance in neurotransmitters, most notably serotonin and dopamine, there are also alterations in functional anatomy that support the concept of EDs as brain disorders. The cause-and-effect relationship in central nervous system alterations in EDs is not clear, nor is their reversibility.

**CLINICAL MANIFESTATIONS**

A central feature of EDs is the overestimation of body size, shape or parts (e.g., abdomen, thighs) leading to weight-control practices intended to reduce weight (AN) or prevent weight gain (BN). Associated practices include severe restriction of caloric intake and behaviors intended to reduce the effect of calories ingested, such as compulsive exercising or purging by inducing vomiting or taking laxatives. Eating and weight loss habits commonly found in EDs can result in a wide range of energy intake and output, the balance of which leads to a wide range in weight from extreme loss of weight in AN to fluctuation around a normal to moderately high weight in BN. Reported eating and weight-control habits (Table 28-4) thus inform the initial primary care approach.

Although weight-control patterns guide the initial pediatric approach, an assessment of commonly reported symptoms and findings on physical examination is essential to identify targets for intervention. When reported symptoms of excessive weight loss (feeling tired and cold; lacking energy; orthostasis; difficulty concentrating) are explicitly linked by the clinician to their associated physical signs (hypothermia with acrocyanosis and slow capillary refill, loss of muscle mass, bradycardia with orthostasis), it becomes more difficult for the patient to deny that a problem exists. Furthermore, awareness that bothersome symptoms can be eliminated by healthier eating and activity patterns can increase a patient’s motivation to engage in treatment. Tables 28-5 and 28-6 detail common symptoms and signs that should be addressed in a pediatric assessment of a suspected ED.

**Differential Diagnosis**

In addition to identifying symptoms and signs that deserve targeted intervention for patients who have an ED or disordered eating, a comprehensive history and physical examination are required in the assessment of a suspected ED to rule out other conditions in the differential diagnosis. Weight loss can occur with any condition in which there is increased catabolism (e.g., malignancy or occult chronic infection) or malabsorption (e.g., inflammatory bowel disease or celiac disease), but these illnesses are generally associated with other findings and are not usually associated with decreased caloric intake. Patients with inflammatory bowel disease can reduce intake to minimize abdominal cramping; eating can cause abdominal discomfort and early satiety in AN because of gastric atony associated with significant weight loss, not malabsorption. Likewise, signs of weight loss in AN might include hypothermia, acrocyanosis with slow capillary refill, and neutropenia suggesting overwhelming sepsis, but the overall picture in EDs is one of relative cardiovascular stability compared to sepsis. Endocrinopathies are also in the differential of EDs. With BN, voracious appetite in the face of weight loss might suggest diabetes mellitus, but blood glucose levels are normal or low in EDs. Adrenal insufficiency mimics

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**Table 28-3** DSM-5 Diagnostic Criteria for Avoidant/Restrictive Food Intake Disorder

<table>
<thead>
<tr>
<th>A. An eating or feeding disturbance (e.g., apparent lack of interest in eating or food; avoidance based on the sensory characteristics of food; concern about aversive consequences of eating) as manifested by persistent failure to meet appropriate nutritional and/or energy needs associated with one (or more) of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Significant weight loss (or failure to achieve expected weight gain or faltering growth in children).</td>
</tr>
<tr>
<td>2. Significant nutritional deficiency.</td>
</tr>
<tr>
<td>3. Dependence on enteral feeding or oral nutritional supplements.</td>
</tr>
<tr>
<td>4. Marked interference with psychosocial functioning.</td>
</tr>
</tbody>
</table>

**B. The disturbance is not better explained by lack of available food or by an associated culturally sanctioned practice.**

**C. The eating disturbance does not occur exclusively during the course of anorexia nervosa or bulimia nervosa, and there is no evidence of a disturbance in the way in which one’s body weight or shape is experienced.**

**D. The eating disturbance is not attributable to a concurrent medical condition or not better explained by another mental disorder.**

When the eating disturbance occurs in the context of another condition or disorder, the severity of the eating disturbance exceeds that routinely associated with the condition or disorder and warrants additional clinical attention.

Specify if:

**In remission:** After full criteria for avoidant/restrictive food intake disorder were previously met, the criteria have not been met for a sustained period of time.


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association between risk factors and disordered eating, with African-American and Caribbean females reporting lower body dissatisfaction and less dieting than Hispanic and non-Hispanic white females. Because peer acceptance is central to healthy adolescent growth and development, especially in early adolescence when AN tends to have its initial prevalence peak, the potential influence of peers on EDs is significant, as are the relationships among peers, body image, and eating. Teasing by peers or by family members (especially male) may be a contributing factor for overweight females.

Family influence in the development of EDs is even more complex because of the interplay of environmental and genetic factors; shared elements of the family environment and immutable genetic factors account for some significant (about equal) variance in disordered eating. There are associations between parents’ and children’s eating behaviors; dieting and physical activity levels suggest parental reinforcement of body-related societal messages. The influence of inherited genetic factors on the emergence of EDs during adolescence is also significant, but not in a direct fashion. Rather, the risk for developing an ED appears to be mediated through a genetic predisposition to anxiety (see Chapter 25), depression (see Chapter 26), or obsessive-compulsive traits that may be modulated through the internal milieu of puberty. There is little evidence that parents “cause” an ED in their child or adolescent; the importance of parents in treatment and recovery cannot be overstated.

**PATHOLOGY AND PATHOGENESIS**

The emergence of EDs coinciding with the processes of adolescence (e.g., puberty, identity, autonomy, cognition) indicates the central role of development. A history of sexual trauma is not significantly more common in EDs than in the population at large, but when present it makes recovery more difficult and is more common in BN. EDs may be viewed as a final common pathway, with a number of predisposing factors that increase the risk of developing an ED, precipitating factors often related to developmental processes of adolescence triggering the emergence of the ED, and perpetuating factors that cause an ED to persist.
### Table 28-4  Eating and Weight Control Habits Commonly Found in Children and Adolescents with an Eating Disorder

<table>
<thead>
<tr>
<th>HABIT</th>
<th>ANOREXIA NERVOSA</th>
<th>BULIMIA NERVOSA</th>
<th>Clinical Comments Regarding Eating Disorder Habits</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall intake</strong></td>
<td>Inadequate energy (calories), although volume of food and beverages may be high because of very low caloric density of intake as a result of “diet” and nonfat choices</td>
<td>Variable, but calories normal to high; intake in binges often “forbidden” food or drink that differs from intake at meals</td>
<td>Consistent inadequate caloric intake leading to wasting of the body is an essential feature of diagnosis</td>
</tr>
<tr>
<td><strong>Food</strong></td>
<td>Counts and limits calories, especially from fat; Emphasis on “healthy food choices” with reduced caloric density</td>
<td>Aware of calories and fat, but less regimented in avoidance than AN</td>
<td>Obsessive-compulsive attention to nutritional data on food labels and may have “logical” reasons for food choices in highly regimented pattern, such as sports participation or family history of lipid disorder</td>
</tr>
<tr>
<td><strong>Beverages</strong></td>
<td>Water or other low- or no-calorie drinks; nonfat milk</td>
<td>Variable, diet soda common; may drink alcohol to excess</td>
<td>Fluids often restricted to avoid weight gain</td>
</tr>
<tr>
<td><strong>Meals</strong></td>
<td>Consistent schedule and structure to meal plan</td>
<td>Meals less regimented and planned than in AN; more likely impulsive and unregulated, often eliminated following a binge-purge episode</td>
<td>Rigid adherence to “rules” governing eating leads to sense of control, confidence, and mastery</td>
</tr>
<tr>
<td><strong>Snacks</strong></td>
<td>Reduced or eliminated from meal plan</td>
<td>Often avoided in meal plans, but then impulsively eaten</td>
<td>Snack foods removed early because “unhealthy”</td>
</tr>
<tr>
<td><strong>Dieting</strong></td>
<td>Initial habit that becomes progressively restrictive, although often appearing superficially “healthy”</td>
<td>Initial dieting gives way to chaotic eating, often interpreted by the patient as evidence of being “weak” or “lazy”</td>
<td>Dieting tends to be impulsive and short-lived, with “diets” often resulting in unintended weight gain</td>
</tr>
<tr>
<td><strong>Binge eating</strong></td>
<td>None in restrictive subtype, but an essential feature in binge-purge subtype</td>
<td>Essential feature, often secretive</td>
<td>Often “subjective” (more than planned but not large)</td>
</tr>
<tr>
<td><strong>Exercise</strong></td>
<td>Characteristically obsessive-compulsive, ritualistic, and progressive</td>
<td>May excel in dance, long-distance running</td>
<td>May be difficult to distinguish active thin vs. ED</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>Characteristic of binge-purge subtype</td>
<td>Most common habit intended to reduce effects of overeating</td>
<td>Physiologic and emotional instability prominent</td>
</tr>
<tr>
<td><strong>Laxatives</strong></td>
<td>May chew, then spit out, rather than swallow, food as a variant</td>
<td>Second most common habit used to reduce or avoid weight gain, often used in increasing doses for cathartic effect</td>
<td>Physiologic and emotional instability prominent</td>
</tr>
<tr>
<td><strong>Diet pills</strong></td>
<td>Very rare, if used; more common in binge-purge subtype</td>
<td>Used to either reduce appetite or increase metabolism</td>
<td>Use of diet pills implies inability to control eating</td>
</tr>
</tbody>
</table>

AN, anorexia nervosa; BN, bulimia nervosa; ED, eating disorder.
<table>
<thead>
<tr>
<th>SYMPTOMS</th>
<th>ANOREXIA NERVOSA</th>
<th>BULIMIA NERVOSA</th>
<th>CLINICAL COMMENTS REGARDING ED SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body image</td>
<td>Feels fat, even with extreme emaciation, often with specific body distortions (e.g., stomach, thighs); Strong drive for thinness, with self-efficacy closely tied to appraisal of body shape, size, and/or weight</td>
<td>Variable body image distortion and dissatisfaction, but drive for thinness is less than the desire to avoid gaining weight</td>
<td>Challenging a patient’s body image is both ineffective and counter-therapeutic clinically Accepting the patient’s expressed body image but noting its discrepancy with symptoms and signs reinforces concept that patient can “feel” fat but also “be” too thin and unhealthy</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hypometabolic symptoms include feeling cold, tired, and weak and lacking energy May be both bothersome and reinforcing</td>
<td>Variable, depending on balance of intake and output and hydration</td>
<td>Symptoms are evidence of body’s “shutting down” in an attempt to conserve calories with an inadequate diet Emphasizing reversibility of symptoms with healthy eating and weight gain can motivate patients to cooperate with treatment</td>
</tr>
<tr>
<td>Skin</td>
<td>Dry skin, delayed healing, easy bruising, goose flesh Orange-yellow skin on hands</td>
<td>No characteristic symptom, self-injurious behavior may be seen</td>
<td>Skin lacks good blood flow and the ability to heal in low weight Carotenemia with large intake of β-carotene foods; reversible</td>
</tr>
<tr>
<td>Hair</td>
<td>Lanugo-type hair growth on face and upper body Slow growth and increased loss of scalp hair</td>
<td>No characteristic symptom</td>
<td>Body hair growth conserves energy Scalp hair loss can worsen during refeeding “telogen effluvium” (resting hair is replaced by growing hair) Reversible with continued healthy eating</td>
</tr>
<tr>
<td>Eyes</td>
<td>No characteristic symptom</td>
<td>Subconjunctival hemorrhage</td>
<td>Caused by increased intrathoracic pressure during vomiting</td>
</tr>
<tr>
<td>Teeth</td>
<td>No characteristic symptom</td>
<td>Erosion of dental enamel erosion Decay, fracture, and loss of teeth</td>
<td>Intraoral stomach acid resulting from vomiting etches dental enamel, exposing softer dental elements</td>
</tr>
<tr>
<td>Salivary glands</td>
<td>No characteristic symptom</td>
<td>Enlargement (no to mild tenderness)</td>
<td>Caused by chronic binge eating and induced vomiting, with parotid enlargement more prominent than submandibular; reversible</td>
</tr>
<tr>
<td>Heart</td>
<td>Dizziness, fainting in restrictive subtype Palpitations more common in binge-purge subtype</td>
<td>Dizziness, fainting, palpitations</td>
<td>Dizziness and fainting due to postural orthostatic tachycardia and dysregulation at hypothalamic and cardiac level with weight loss, as a result of hypovolemia with binge-purge Palpitations and arrhythmias often caused by electrolyte disturbance Symptoms reverse with weight gain and/or cessation of binge-purge</td>
</tr>
<tr>
<td>Abdomen</td>
<td>Early fullness and discomfort with eating Constipation Perceives contour as “fat,” often preferring well-defined abdominal musculature</td>
<td>Discomfort after a binge Cramps and diarrhea with laxative abuse</td>
<td>Weight loss is associated with reduced volume and tone of GI tract musculature, especially the stomach Laxatives may be used to relieve constipation or as a cathartic Symptom reduction with healthy eating can take weeks to occur</td>
</tr>
<tr>
<td>Extremities and musculoskeletal</td>
<td>Cold, blue hands and feet</td>
<td>No characteristic symptoms Self-cutting or burning on wrists or arms</td>
<td>Energy-conserving low body temperature with slow blood flow most notable peripherally Quickly reversed with healthy eating</td>
</tr>
<tr>
<td>Nervous system</td>
<td>No characteristic symptom</td>
<td>No characteristic symptom</td>
<td>Neurologic symptoms suggest a diagnosis other than an ED</td>
</tr>
<tr>
<td>Mental status</td>
<td>Depression, anxiety, obsessive-compulsive symptoms, alone or in combination</td>
<td>Depression; PTSD; borderline personality disorder traits</td>
<td>Underlying mood disturbances can worsen with dysfunctional weight control practices and can improve with healthy eating AN patients might report emotional “numbness” with starvation, preferable to emotionality associated with healthy eating</td>
</tr>
</tbody>
</table>

AN, anorexia nervosa; BN, bulimia nervosa; ED, eating disorder; GI, gastrointestinal; PTSD, posttraumatic stress disorder.
<table>
<thead>
<tr>
<th>PHYSICAL SIGN</th>
<th>RESTRICTIVE INTAKE</th>
<th>BINGE EATING/PURGING</th>
<th>CLINICAL COMMENTS RELATED TO EATING DISORDER SIGNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>General appearance</td>
<td>Thin to cachetic, depending on balance of intake and output. Might wear bulky clothing to hide thinness and might resist being examined.</td>
<td>Thin to overweight, depending on the balance of intake and output through various means.</td>
<td>Examine in hospital gown. Weight loss more rapid with reduced intake and excessive exercise. Binge eating can result in large weight gain, regardless of purging behavior. Appearance depends on balance of intake and output and overall weight control habits.</td>
</tr>
<tr>
<td>Weight</td>
<td>Low and falling (if previously overweight may be normal or high); may be falsely elevated if patient drinks fluids or adds weights to body before being weighed.</td>
<td>Highly variable, depending on balance of intake and output and state of hydration. Falsification of weight is unusual.</td>
<td>Weigh in hospital gown with no underwear, after voiding (measure urine SG). Remain in gown until physical exam completed to identify possible fluid loading (low urine SG, palpable bladder) or adding weights to body.</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hypothermia: temp &lt; 35.5°C (95.9°F), pulse &lt; 60 beats/min. Slowed psychomotor response with very low core temperature.</td>
<td>Variable, but hypometabolic state is less common than in AN.</td>
<td>Hypometabolism related to disruption of hypothalamic control mechanisms as a result of weight loss. Signs of hypometabolism (cold skin, slow capillary refill, acrocyanosis) most evident in hands and feet, where energy conservation is most active.</td>
</tr>
<tr>
<td>Hair</td>
<td>Lanugo-type hair growth on face and upper body. Scalp hair loss, especially prominent in parietal region.</td>
<td>No characteristic sign.</td>
<td>Body hair growth conserves energy. Scalp hair loss “telogen effluvium” can worsen weeks after refeeding begins, as hair in resting phase is replaced by growing hair.</td>
</tr>
<tr>
<td>Eyes</td>
<td>No characteristic sign.</td>
<td>Subconjunctival hemorrhage.</td>
<td>Increased intrathoracic pressure during vomiting.</td>
</tr>
<tr>
<td>Teeth</td>
<td>No characteristic sign.</td>
<td>Eroded dental enamel and decayed, fractured, missing teeth.</td>
<td>Perimolysis, worse on lingual surfaces of maxillary teeth, is intensified by brushing teeth without preceding water rinse.</td>
</tr>
<tr>
<td>Salivary glands</td>
<td>No characteristic sign.</td>
<td>Enlargement, relatively nontender.</td>
<td>Parotid &gt; submandibular involvement with frequent and chronic binge eating and induced vomiting.</td>
</tr>
<tr>
<td>Throat</td>
<td>No characteristic sign.</td>
<td>Absent gag reflex.</td>
<td>Extinction of gag response with repeated pharyngeal stimulation.</td>
</tr>
<tr>
<td>Heart</td>
<td>Bradycardia, hypotension, and orthostatic pulse differential &gt; 25 beats/min.</td>
<td>Hypovolemia if dehydrated.</td>
<td>Changes in AN resulting from central hypothalamic and intrinsic cardiac function. Orthostatic changes less prominent if athletic, more prominent if associated with purging.</td>
</tr>
<tr>
<td>Abdomen</td>
<td>Scaphoid, organs may be palpable but not enlarged, stool-filled left lower quadrant.</td>
<td>Increased bowel sounds if recent laxative use.</td>
<td>Presence of organomegaly requires investigation to determine cause. Constipation prominent with weight loss.</td>
</tr>
<tr>
<td>Extremities and musculoskeletal system</td>
<td>Cold, acrocyanosis, slow capillary refill. Edema of feet. Loss of muscle, subcutaneous, and fat tissue.</td>
<td>No characteristic sign, but may have rebound edema after stopping chronic laxative use.</td>
<td>Signs of hypometabolism (cold) and cardiovascular dysfunction (slow capillary refill and acrocyanosis) in hands and feet. Edema, caused by capillary fragility more than hypoproteinemina in AN, can worsen in early phase of refeeding.</td>
</tr>
<tr>
<td>Nervous system</td>
<td>No characteristic sign.</td>
<td>No characteristic sign.</td>
<td>Water loading before weigh-ins can cause acute hyponatremia.</td>
</tr>
<tr>
<td>Mental status</td>
<td>Anxiety about body image, irritability, depressed mood, oppositional to change.</td>
<td>Depression, evidence of PTSD, more likely suicidal than AN.</td>
<td>Mental status often improves with healthier eating and weight; SSRIs only shown to be effective for BN.</td>
</tr>
</tbody>
</table>

AN, anorexia nervosa; BN, bulimia nervosa; PTSD, posttraumatic stress disorder; SG, specific gravity; SSRI, selective serotonin reuptake inhibitor.
many physical symptoms and signs found in restrictive AN but is associated with elevated potassium levels and hyperpigmentation. Although thyroid disorders are often considered, because of changes in weight and other symptoms in AN, the overall presentation includes symptoms of both underactive and overactive thyroid, such as hypothermia, bradycardia, and constipation, as well as weight loss and excessive physical activity, respectively.

In the central nervous system, craniohypobryngiomas and Rathke pouch tumors can mimic some of the findings of AN, such as weight loss and growth failure, and even some body image disturbances, but the latter are less fixed than in typical EDs and are associated with other findings, including evidence of increased intracranial pressure. Mitochondrial neurogastrointestinal encephalomyopathy, caused by a mutation in the MYM gene, presents with gastrointestinal dysmotility, cachexia, ptosis, peripheral neuropathy, ophthalmoplegia, and leukoencephalopathy. Symptoms begin during the second decade of life and are often initially diagnosed as AN. Early satiety, vomiting, cramps, constipation, and pseudoobstruction result in weight loss often before the neurologic features are noticed.

Any patient with an atypical presentation of an ED, based on age, sex, or other factors not typical for AN or BN deserves a scrupulous search for an alternative explanation. Patients can have both an underlying illness and an ED. The core features of dysfunctional eating habits—body image disturbance and change in weight—can coexist with conditions such as diabetes mellitus, where patients might manipulate their insulin dosing to lose weight.

LABORATORY FINDINGS
Because the diagnosis of an ED is made clinically, there is no confirmatory laboratory test. Laboratory abnormalities, when found, are the result of malnutrition, weight-control habits used, or medical complications; studies should be chosen based on history and physical examination. A routine screening battery typically includes complete blood count, erythrocyte sedimentation rate (should be normal), and biochemical profile. Common abnormalities in ED include low white blood cell count with normal hemoglobin and differential; hypokalemia, hypochloremic metabolic alkalosis with severe vomiting; mildly elevated liver enzymes, cholesterol, and cortisol levels; low gonadotropins and blood glucose with marked weight loss; and generally normal total protein, albumin, and renal function. An electrocardiogram may be useful when profound bradycardia or arrhythmia is detected; the electrocardiogram usually has low voltage, with nonspecific ST or T wave changes. Although prolonged QTc has been reported, prospective studies have not found an increased risk for this.

COMPLICATIONS
No organ is spared the harmful effects of dysfunctional weight-control habits, but the most concerning targets of medical complications are the heart, brain, gonads, and bones. Some heart findings in EDs (e.g., sinus bradycardia and hypotension) are physiologic adaptations to starvation that conserve calories and reduce afterload. Cold, blue hands and feet with slow capillary refill that can result in tissue perfusion insufficient to meet demands also represent energy-conserving responses associated with inadequate intake. All of these acute changes are reversible with restoration of nutrition and weight. Significant orthostatic pulse changes, prolonged corrected QT interval, ventricular dysrhythmias, or reduced myocardial contractility reflect myocardial impairment that can be lethal. In addition, with extremely low weight, refeeding syndrome (a result of the rapid drop in serum phosphorous, magnesium, and potassium with excessive reintroduction of calories, especially carbohydrates), is associated with acute heart failure and neurologic symptoms. With long-term malnutrition, the myocardium appears to be more prone to tachyarrhythmias, the second most common cause of death after suicide. In BN, dysrhythmias can also be related to electrolyte imbalance.

Clinically, the primary brain area affected acutely in EDs, especially with weight loss, is the hypothalamus. Hypothalamic dysfunction is reflected in problems with thermoregulation (warming and cooling), satiety, sleep, autonomic cardioregulatory imbalance (orthostasis), and endocrine function (reduced gonadal and excessive adrenal cortex stimulation), all of which are reversible. Anatomic studies of the brain in ED have focused on AN, with the most common finding being increased ventricular and sulcal volumes that normalize with weight restoration. Persistent gray-matter deficits following recovery, related to the degree of weight loss, have been reported. Elevated medial temporal lobe cerebral blood flow on positron emission tomography similar to that found in psychotic patients, suggests that these changes may be related to body image distortion. Also, visualizing high-calorie foods is associated with exaggerated responses in the visual association cortex that are similar to those seen in patients with specific phobias. Patients with AN might have an imbalance between serotonin and dopamine pathways related to neurocircuits in which dietary restraint reduces anxiety.

Reduced gonadal function occurs in male and female patients; it is clinically manifested in AN as amenorrhea in female patients and erectile dysfunction in males. It is related to understimulation from the hypothalamus as well as cortical suppression related to physical and emotional stress. Amenorrhea precedes significant dieting and weight loss in up to 30% of females with AN, and most adolescents with EDs perceive the absence of menses positively. The primary health concern is the negative effect of decreased ovarian function and estrogen on bones. Decreased bone mineral density (BMD) with osteopenia or the more severe osteoporosis is a significant complication of EDs (more pronounced in AN than BN). Data do not support the use of sex hormone replacement therapy because this alone does not improve other causes of low BMD (low body weight, lean body mass, and insulin-like growth factor-1; high cortisol).

TREATMENT
Principles Guiding Primary Care Treatment
The approach in primary care should facilitate the acceptance by the patient (and parents) of the diagnosis and initial treatment recommendations. A nurturant-authoritative approach using the biopsychosocial model is useful. A pediatrician who explicitly acknowledges that the patient may disagree with the diagnosis and treatment recommendations and be ambivalent about changing eating habits, while also acknowledging that recovery requires strength, courage, will-power and determination, demonstrates nurturance. Parents also find it easier to be nurturant once they learn that the development of an ED is neither a willful decision by the patient nor a reflection of bad parenting. Framing the ED as a coping mechanism for a complex variety of issues with both positive and negative aspects avoids blame or guilt and can prepare the family for professional help that will focus on strengths and restoring health, rather than on the deficits in the adolescent or the family.

The authoritative aspect of a physician's role comes from expertise in health, growth, and physical development. A goal of primary care treatment should be attaining and maintaining health—not merely weight gain—although weight gain is a means to the goal of wellness. Providers who frame themselves as consultants to the patient with authoritative knowledge about health can avoid a countertherapeutic authoritarian stance. Primary care health-focused activities include monitoring the patient's physical status, setting limits on behaviors that threaten the patient's health, involving specialists with expertise in EDs on the treatment team, and continuing to provide primary care for health maintenance, acute illness, or injury.

The biopsychosocial model uses a broad ecologic framework, starting with the biologic impairments of physical health related to dysfunctional weight control practices, evidenced by symptoms and signs. Explicitly linking ED behaviors to symptoms and signs can increase motivation to change. In addition, there are usually unresolved psychosocial conflicts in both the intrapersonal (self-esteem, self-efficacy) and interpersonal (family, peers, school) domains. Weight-control practices initiated as coping mechanisms become reinforced because of positive feedback. That is, external rewards (e.g., compliments about improved physical appearance) and internal rewards (e.g., perceived mastery over what is eaten or what is done to minimize the effects of overeating through exercise or purging) are more powerful to maintain
behavior than negative feedback (e.g., conflict with parents, peers, and others about eating) is to change it. Thus, when definitive treatment is initiated, more productive alternative means of coping must be developed.

**Nutrition and Physical Activity**

The primary care provider generally begins the process of prescribing nutrition, although a dietician should be involved eventually in the meal planning and nutritional education of patients with AN or BN. Framing food as fuel for the body and the source of energy for daily activities emphasizes the health goal of increasing the patient’s energy level, endurance, and strength. For patients with AN and low weight, the nutrition prescription should work toward gradually increasing weight at the rate of about 0.5-1 lb/wk, by increasing energy intake by 100-200 kcal increments every few days toward a target of approximately 90% of average body weight for sex, height, and age. Weight gain will not occur until intake exceeds output, and eventual intake for continued weight gain can exceed 4,000 kcal/day, especially for patients who are anxious and have high levels of thermogenesis from nonexercise activity. Stabilizing intake is the goal for patients with BN, with a gradual introduction of forbidden foods while also limiting foods that might trigger a binge.

When initiating treatment of an ED in a primary care setting, the clinician should be aware of common cognitive patterns. Patients with AN typically have all-or-none thinking (related to perfectionism) with a tendency to overgeneralize and jump to catastrophic conclusions, while assuming that their body is governed by rules that do not apply to others. These tendencies lead to the dichotomization of foods into good or bad categories, having a day ruined because of an unexpected event, or choosing foods based on rigid self-imposed restrictions. These thoughts may be related to neurocircuitry and neurotransmitter abnormalities related to executive function and rewards.

A standard nutritional balance of 15-20% calories from protein, 50-55% from carbohydrate, and 25-30% from fat is appropriate. The fat content may need to be lowered to 15-20% early in the treatment of AN because of continued fat phobia. With the risk of low BMD in patients with AN, calcium and vitamin D supplements are often needed to attain the recommended 1,300 mg/day intake of calcium. Refeeding can be accomplished with frequent small meals and snacks consisting of a variety of foods and beverages (with minimal diet or fat-free products), rather than fewer high-volume high-calorie meals. Some patients find it easier to take in part of the additional nutrition as canned supplements (medicine) rather than food. Regardless of the source of energy intake, the risk for refeeding syndrome (acute tachycardia and heart failure with neurologic symptoms associated primarily with acute decline in serum phosphate and magnesium) increases with the degree of weight loss and the rapidity of caloric increases. Therefore, if the weight has fallen below 80% of expected weight for height, refeeding should proceed cautiously, possibly in the hospital (Table 28-7).

Patients with AN tend to have a highly structured day with restrictive intake, in contrast to BN, which is characterized by a lack of structure, resulting in chaotic eating patterns and binge-purge episodes. All patients with AN, BN, or ED-NOS benefit from a daily structure for healthy eating that includes 3 meals and at least 1 snack a day, distributed evenly over the day, based on balanced meal planning. Breakfast deserves special emphasis because it is often the first meal eliminated in AN and is often avoided the morning after a binge-purge episode in BN. In addition to structuring meals and snacks, patients should plan structure in their activities. Although overexercising is common in AN, completely prohibiting exercise can lead to further restriction of intake or to surreptitious exercise; inactivity should be limited to situations in which weight loss is dramatic or there is physiologic instability. Also, healthy exercise (once a day, for no more than 30 minutes, at no more than moderate intensity) can improve mood and make increasing calories more acceptable. Because patients with AN often are unaware of their level of activity and tend toward progressively increasing their output, exercising without either a partner or supervision is not recommended.

**Table 28-7** Indications for Inpatient Medical Hospitalization of Patients with Anorexia Nervosa

<table>
<thead>
<tr>
<th>PHYSICAL AND LABORATORY</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate &lt; 50 beats/min</td>
<td></td>
</tr>
<tr>
<td>Other cardiac rhythm disturbances</td>
<td></td>
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<tr>
<td>Blood pressure &lt; 80/50 mm Hg</td>
<td></td>
</tr>
<tr>
<td>Postural hypotension resulting in a &gt;10 mm Hg drop or a &gt;25 beats/min increase</td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
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<tr>
<td>Hypophosphatemia</td>
<td></td>
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<tr>
<td>Hypoglycemia</td>
<td></td>
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<tr>
<td>Dehydration</td>
<td></td>
</tr>
<tr>
<td>Body temperature &lt; 36.1°C (97°F)</td>
<td></td>
</tr>
<tr>
<td>&lt;80% healthy body weight</td>
<td></td>
</tr>
<tr>
<td>Hepatic, cardiac, or renal compromise</td>
<td></td>
</tr>
</tbody>
</table>

**PSYCHIATRIC**

Suicidal intent and plan

Very poor motivation to recover (in family and patient)

Preoccupation with ego-syntonic thoughts

Coexisting psychiatric disorders

**MISCELLANEOUS**

Requires supervision after meals and while using the restroom

Failed day treatment

**Primary Care Treatment**

Follow-up primary care visits are essential in the management of EDs; close monitoring of the response of the patient and the family to suggested interventions is required to determine which patients can remain in primary care treatment (patients with early, mildly disordered eating), which patients need to be referred to individual specialists for co-management (mildly progressive disordered eating), and which patients need to be referred for interdisciplinary team management (EDs). Between the initial and subsequent visits, the patient can record daily caloric intake (food, drink, amount, time, location), physical activity (type, duration, intensity), and emotional state (e.g., angry, sad, worried) in a journal that is reviewed jointly with the patient in follow-up. Focusing on the recorded data helps the clinician to identify dietary and activity deficiencies and excesses as well as behavioral and mental health patterns, and the patient to become objectively aware of the relevant issues to address in recovery.

Given the tendency of patients with AN to overestimate their caloric intake and underestimate their activity level, before reviewing the journal record it is important at each visit to measure weight, without underclothing in a hospital gown after voiding; urine specific gravity; temperature; and blood pressure and pulse in supine, sitting, and standing positions as objective data. In addition, a targeted physical examination focused on hypometabolism, cardiovascular stability, and mental status, as well as any related symptoms, should occur at each visit to monitor progress (or regression).

**Referral to Mental Health Services**

In addition to referral to a registered dietitian, mental health services are an important element of treatment of EDs. Depending on availability and experience, these services can be provided by a psychiatric social worker, psychologist, or psychiatrist, who should team with the primary care provider. Although patients with AN often are prescribed a selective serotonin reuptake inhibitor (SSRI) because of depressive symptoms, there is no evidence of efficacy for patients at low weight; food remains the initial treatment of choice to treat depression in AN. SSRIs, very effective in reducing binging-purge behaviors regardless of depression, are considered a standard element of therapy in BN. SSRI dosage in BN, however, may need to increase to an equivalent of more than 60 mg of fluoxetine to maintain effectiveness.

Cognitive-behavioral therapy, which focuses on restructuring “thinking errors” and establishing adaptive patterns of behavior, is more effective than interpersonal or psychoanalytic approaches.
Dialectical behavioral therapy, in which distorted thoughts and emotional responses are challenged, analyzed, and replaced with healthier ones, with an emphasis on “mindfulness,” requires adult thinking skills and is useful for older patients with BN. Group therapy can provide much needed support, but it requires a skilled clinician. Combining patients at various levels of recovery who experience variable reinforcement from dysfunctional coping behaviors can be challenging if group therapy patients compete with each other to be “thinner” or take up new behaviors such as vomiting.

The younger the patient, the more intimately the parents need to be involved in therapy. The only treatment approach with evidence-based effectiveness in the treatment of AN in children and adolescents is family-based treatment, exemplified by the Maudsley approach. This 3-phase intensive outpatient model helps parents play a positive role in restoring their child’s eating and weight to normal, then returns control of eating to the child who has demonstrated the ability to maintain healthy weight, and then encourages healthy progression in the other domains of adolescent development. Features of effective family treatment include an agnostic approach in which the cause of the disease is unknown and irrelevant to weight gain, emphasizing that parents are not to blame for EDs; parents being actively nurturing and supportive of their child’s healthy eating while reinforcing limits on dysfunctional habits, rather than an authoritarian food police or complete hands-off approach; and reinforcement of parents as the best resource for recovery for almost all patients, with professionals serving as consultants and advisors to help parents address challenges.

**Referral to an Interdisciplinary Eating Disorder Team**

The treatment of a child or adolescent diagnosed with an ED is ideally provided by an interdisciplinary team (physician, nurse, dietitian, mental health provider) with expertise treating pediatric patients. Because such teams, often led by specialists in adolescent medicine at medical centers, are not widely available, the primary care provider might need to convene such a team. Adolescent medicine–based programs report encouraging treatment outcomes, possibly related to patients entering earlier into care and the stigma that some patients and parents may associate with psychiatry-based programs. Specialty centers focused on treating EDs are generally based in psychiatry and often have separate tracks for younger and adult patients. The elements of treatment noted earlier (cognitive-behavioral therapy, dialectical behavioral therapy, and family-based therapy), as well as individual and group treatment should all be available as part of interdisciplinary team treatment. Comprehensive services ideally include intensive outpatient and/or partial hospitalization as well as inpatient treatment. Regardless of the intensity, type, or location of the treatment services, the patient, parents, and primary care provider are essential members of the treatment team. A recurring theme in effective treatment is helping patients and families re-establish connections that are disrupted by the ED.

**Inpatient** medical treatment of EDs is generally limited to patients with AN, to stabilize and treat life-threatening starvation and to provide supportive mental health services. Inpatient medical care may be required to avoid refeeding syndrome in severely malnourished patients, provide nasogastric tube feeding for patients unable or unwilling to eat, or initiate mental health services, especially family-based treatment, if this has not occurred on an outpatient basis (see Table 28-7). Admission to a general pediatric or hospital unit is advised only for short-term stabilization in preparation for transfer to a medical unit with expertise in treating pediatric EDs. Inpatient psychiatric care of EDs should be provided on a unit with expertise in managing the often challenging behaviors (e.g., hiding or discarding food, vomiting, surreptitious exercise) and emotional problems (e.g., depression, anxiety). Suicidal risk is small, but patients with AN might threaten suicide if made to eat or gain weight in an effort to get their parents to back off. An ED partial hospital program offers outpatient services that are less intensive than round-the-clock inpatient care. Generally held 4-5 days a wk for 6 to 9 hr each session, partial hospital program services typically are group-based and include eating at least 2 meals as well as opportunities to address issues in a setting that more closely approximates “real life” than inpatient treatment. That is, patients sleep at home and are free-living on weekends, exposing them to challenges that can be processed during the 25-40 hr in program, also sharing group and family experiences.

**Supportive Care**

In relation to pediatric EDs, support groups are primarily designed for parents. Because their daughter or son with an ED often resists the diagnosis and treatment, parents often feel helpless and hopeless. Because of the historical precedent of blaming parents for causing EDs, parents often express feelings of shame and isolation (www.maudsleyparents.org). Support groups and multifamily therapy sessions bring parents together with other parents whose families are at various stages of recovery from an ED in ways that are educational and encouraging. Patients often benefit from support groups after intensive treatment or at the end of treatment because of residual body image or other issues after eating and weight have normalized.

**PROGNOSIS**

With early diagnosis and effective treatment, 80% or more of youth with AN recover: They develop normal eating and weight control habits, resume menses, maintain average weight for height, and function in school, work, and relationships, although some still have poor body image. With weight restoration, fertility returns as well, although the weight for resumption of menses (approximately 92% of average body weight for height) may be lower than the weight for ovulation. The prognosis for BN is less well established, but outcome improves with multidimensional treatment that includes SSRIs and attention to mood, past trauma, impulsivity, and any existing psychopathology. Atypical AN and ED-NOS may still have significant morbidity.

**PREVENTION**

Given the complexity of the pathogenesis of EDs, prevention is difficult. Targeted preventive interventions can reduce risk factors in older adolescents and college-age women. Universal prevention efforts to promote healthy weight regulation and discourage unhealthy dieting have not shown effectiveness in middle-school students. Programs that include recovered patients or focus on the problems associated with EDs can inadvertently normalize or even glamorize EDs and should be discouraged.

Bibliography is available at Expert Consult.
Bibliography
Chapter 29
Disruptive, Impulse-Control, and Conduct Disorders
Heather J. Walter, Asma Rashid, Lovern R. Moseley, and David R. DeMaso

The disruptive, impulse-control, and conduct disorders are interrelated sets of psychiatric symptoms characterized by a core deficit in self-regulation of anger, aggression, defiance, and antisocial behaviors. The disruptive, impulse-control, and conduct disorders include oppositional defiant, intermittent explosive, conduct, other specified/unspecified disruptive, impulse control, and conduct, and antisocial personality disorders, as well as pyromania and kleptomania.
**Table 29-1 DSM-5 Diagnostic Criteria for Oppositional Defiant Disorder**

A. A pattern of angry/irritable mood, argumentative/defiant behavior, or vindictiveness lasting at least 6 mo as evidenced by at least 4 symptoms from any of the following categories, and exhibited during interaction with at least 1 individual who is not a sibling.

**Angry/Irritable Mood**

1. Often loses temper.
2. Is often touchy or easily annoyed.
3. Is often angry and resentful.

**Argumentative/Defiant Behavior**

4. Often argues with authority figures or, for children and adolescents, with adults.
5. Often actively defies or refuses to comply with requests from authority figures or with rules.
6. Often deliberately annoys others.
7. Often blames others for his or her mistakes or misbehavior.

**Vindictiveness**

8. Has been spiteful or vindictive at least twice within the past 6 mo.

**Note:** The persistence and frequency of these behaviors should be used to distinguish a behavior that is within normal limits from a behavior that is symptomatic. For children younger than 5 yr, the behavior should occur on most days for a period of at least 6 mo unless otherwise noted (Criterion A8). For individuals 5 yr or older, the behavior should occur at least once per week for at least 6 mo, unless otherwise noted (Criterion A8). While these frequency criteria provide guidance on a minimal level of frequency to define symptoms, other factors should be considered, such as whether the frequency and intensity of the behaviors are outside a range that is normative for the individual's developmental level, gender, and culture.

B. The disturbance in behavior is associated with distress in the individual or others in his or her immediate social context (e.g., family, peer group, work colleagues), or it impacts negatively on social, educational, occupational, or other important areas of functioning.

C. The behaviors do not occur exclusively during the course of a psychotic, substance use, depressive, or bipolar disorder. Also, the criteria are not met for disruptive mood dysregulation disorder.

**Table 29-2 DSM-5 Diagnostic Criteria for Intermittent Explosive Disorder**

A. Recurrent behavioral outbursts representing a failure to control aggressive impulses as manifested by either of the following:

1. Verbal aggression (e.g., temper tantrums, tirades, verbal arguments or fights) or physical aggression toward property, animals, or other individuals, occurring twice weekly, on average, for a period of 3 mo. The physical aggression does not result in damage or destruction of property and does not result in physical injury to animals or other individuals.

2. Three behavioral outbursts involving damage or destruction of property and/or physical assault involving physical injury against animals or other individuals occurring with a 12-mo period.

**Note:** The magnitude of aggressiveness expressed during the recurrent outbursts is grossly out of proportion to the provocation or to any precipitating psychosocial stressors.

B. The recurrent aggressive outbursts cause either marked distress in the individual or impairment in occupational or interpersonal functioning, or as associated with financial or legal consequences.

C. The recurrent aggressive outbursts are not premeditated (i.e., they are impulsive and/or anger-based) and are not committed to achieve some tangible objective (e.g., money, power, intimidation).

D. The recurrent aggressive outbursts cause either marked distress in the individual or impairment in occupational or interpersonal functioning, or as associated with financial or legal consequences.

E. Chronological age is at least 6 yr (or equivalent developmental level).

F. The recurrent aggressive outbursts are not better explained by another mental disorder (e.g., major depressive disorder, bipolar disorder, disruptive mood dysregulation disorder, a psychotic disorder, antisocial personality disorder, borderline personality disorder) and are not attributable to another medical condition (e.g., head trauma, Alzheimer disease) or to the physiologic effects of a substance (e.g., a drug of abuse, a medication). For children ages 6-18 yr, aggressive behavior that occurs as part of an adjustment disorder should not be considered for this diagnosis.

**Note:** This diagnosis can be made in addition to the diagnosis of attention-deficit/hyperactivity disorder, conduct disorder, oppositional defiant disorder, or autism spectrum disorder when recurrent impulsive aggressive outbursts are in excess of those usually seen in these disorders and warrant clinical attention.

**DESCRIPTION**

**Oppositional defiant disorder (ODD)** is characterized by a pattern lasting at least 6 mo of angry, irritable mood, argumentative/defiant behavior, or vindictiveness exhibited during interaction with at least 1 individual who is not a sibling (Table 29-1). For preschool children, the behavior must occur on most days whereas in school-age children, the behavior must occur at least once a week. The severity of the disorder is considered to be mild if symptoms are confined to only 1 setting (e.g., at home, at school, with peers), moderate if symptoms are present in at least 2 settings, and severe if symptoms are present in 3 or more settings.

**Intermittent explosive disorder (IED)** is characterized by recurrent verbal or physical aggression that is grossly disproportionate to the provocation or to any precipitating psychosocial stressors (Table 29-2). The outbursts, which are impulsive and/or anger-based rather than premeditated and/or instrumental, typically last for less than 30 min and commonly occur in response to a minor provocation by a close intimate.

**Conduct disorder (CD)** is characterized by a repetitive and persistent pattern over at least 12 mo of serious rule-violating behavior in which the basic rights of others or major societal norms or rules are violated (Table 29-3). The symptoms of CD are divided into 4 major categories: aggression to people and animals, destruction of property, deceitfulness or theft, and serious rule violations (e.g., truancy, running away). Three subtypes of CD (which have different prognostic significance) are based on the age of onset: childhood-onset type, adolescent onset type, and unspecified. A small proportion of individuals with CD exhibit characteristics (lack of remorse/guilt, callous/lack of empathy, unconcerned about performance, shallow/deficient affect) that qualify for the “with limited prosocial emotions” specifier. CD is classified as mild if few if any symptoms in excess of those required for the diagnosis are present, and the symptoms cause relatively minor harm to others. CD is classified as severe if many symptoms in excess of those required for the diagnosis are present, and the symptoms cause considerable harm to others. Moderate severity is intermediate between mild and severe.

**Other specified/unspecified disruptive, impulse-control, and CD (subsyndromal disorder)** applies to presentations in which symptoms characteristic of the disorders in this class are present and cause clinically significant distress or functional impairment, but do not meet full diagnostic criteria for any of the disorders in this class.

**Epidemiology**

The prevalence of ODD approximates 3% and in preadolescents is more common in males than females (1.4:1). One-year prevalence rates for IED and CD approximate 3% and 4%, respectively. For CD, prevalence rates rise from childhood to adolescence and are higher...
among males than among females. The prevalence of these disorders has been shown to be higher in lower socioeconomic classes.

**CLINICAL COURSE**

Oppositional behavior can occur in all children and adolescents from time to time, particularly during the toddler and early teenage periods when autonomy and independence are normative developmental tasks. Oppositional behavior becomes a concern when it is intense, persistent, and pervasive and when it affects the child’s social, family, and academic life.

Some of the earliest manifestations of oppositionality are stubbornness (3 yr), defiance and temper tantrums (4-5 yr), and argumentativeness (6 yr). Approximately 65% of children with ODD exit from the diagnosis after a 3 yr follow-up; earlier age at onset of oppositional symptoms conveys a poorer prognosis. ODD often precedes the development of CD (approximately 30% higher likelihood with comorbid attention-deficit/hyperactivity disorder [ADHD; see Chapter 33]), but also increases the risk for the development of depressive and anxiety disorders. The defiant and vindictive symptoms carry most of the risk for CD, whereas the angry-irritable mood symptoms carry most of the risk for anxiety and depression.

IED most commonly begins in late childhood or adolescence and appears to follow a chronic and persistent course over many years. The defiant and vindictive symptoms carry most of the risk for adulthood; in a substantial fraction, antisocial personality disorder develops. Individuals with CD also are at risk for the later development of mood, anxiety, posttraumatic stress, impulse control, psychotic, somatic symptom, and substance-related disorders.

**DIFFERENTIAL DIAGNOSIS**

The disorders in this diagnostic class share a number of characteristics with each other as well as with disorders from other classes, and as such must be carefully differentiated. ODD can be distinguished from CD by the absence of physical aggression and destructiveness, and by the presence of angry/irritable mood; ODD can be distinguished from IED by the lack of serious aggression (physical assault). IED can be distinguished from CD by the lack of predatory aggression and other nonaggressive symptoms of CD.

The oppositionality seen in ODD must be distinguished from that seen in ADHD, depressive and bipolar disorders (including disruptive mood dysregulation disorder [see Chapter 26]), language disorders and intellectual disability, and social anxiety disorder. ODD should not be diagnosed if the behaviors occur exclusively during the course of a psychotic, substance use, depressive or bipolar disorder, and if criteria are met for disruptive mood dysregulation disorder. IED should not be diagnosed if the behavior can be better explained by a depressive, bipolar, disruptive mood dysregulation, psychotic, antisocial personality, or borderline personality disorder. The aggression seen in CD must be distinguished from that seen in ADHD and intermittent explosive, depressive, bipolar, and adjustment disorders.

**COMORBIDITY**

Rates of ODD are much higher in children with ADHD, which suggests shared temperamental risk factors. Depressive, anxiety, and substance use disorders are most commonly comorbid with IED. ADHD and ODD are both common in individuals with CD, and this comorbid presentation predicts worse outcomes. CD also may co-occur with anxiety, depressive, bipolar, learning, language, and substance-related disorders.

**SEQUELAE**

The disruptive, impulse-control, and CDs are associated with a wide range of psychiatric disorders in adulthood and with many other adverse outcomes, such as suicidal behavior, physical injury, delinquency and criminality, legal problems, substance use, unplanned pregnancy, social instability, marital failure, and academic and occupational underachievement.

**ETIOLOGY AND RISK FACTORS**

At the individual level, a number of neurobiologic markers (lower heart rate and skin conductance reactivity, reduced basal cortisol reactivity, abnormalities in the prefrontal cortex and amygdala, serotoninergic abnormalities) have been variously associated with aggressive behavior disorders. Other biologic risk factors include pre-, peri-, and postnatal insults, cognitive and linguistic impairment (particularly language-based learning deficits); difficult temperamental characteristics (particularly negative affectivity, poor frustration tolerance, impulsivity); certain personality characteristics (novelty seeking, reduced harm avoidance, and reward dependence); and certain cognitive characteristics (cognitive rigidity, hostile attributions for ambiguous social cues).

At the family level, a consistently demonstrated risk factor is ineffective parenting. Parents of behaviorally disordered children have been found to be more inconsistent in their use of rules; to issue more and unclear commands; to be more likely to respond to their child on the basis of their mood rather than the child’s behavior; to be less

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**Table 29-3** DSM-5 Diagnostic Criteria for Conduct Disorder

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>DSM-5 Criteria</th>
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<tbody>
<tr>
<td>A. A repetitive and persistent pattern of behavior in which the basic rights of others or major age-appropriate societal norms or rules are violated, as manifested by the presence of at least 3 of the following 15 criteria in the past 12 mo from any of the categories below, with at least 1 criterion present in the past 6 mo:</td>
<td></td>
</tr>
<tr>
<td>1. Often bullies, threatens, or intimidates others.</td>
<td></td>
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<tr>
<td>2. Often initiates physical fights.</td>
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<tr>
<td>3. Has used a weapon that can cause serious physical harm to others (e.g., a bat, brick, broken bottle, knife, gun).</td>
<td></td>
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<tr>
<td>4. Has been physically cruel to people.</td>
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<tr>
<td>5. Has been physically cruel to animals.</td>
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<tr>
<td>6. Has stolen while confronting a victim (e.g., mugging, purse snatching, extortion, armed robbery).</td>
<td></td>
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<tr>
<td>7. Has forced someone into sexual activity.</td>
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</tr>
<tr>
<td>B. The disturbance in behavior causes clinically significant impairment in social, academic, or occupational functioning.</td>
<td></td>
</tr>
<tr>
<td>C. If the individual is age 18 yr or older, criteria are not met for antisocial personality disorder.</td>
<td></td>
</tr>
</tbody>
</table>

likely to monitor their children's whereabouts; and to be relatively unresponsive to their children's prosocial behavior. Complicating this association is the consistent finding that temperamentally difficult children are more likely to elicit negative parenting responses, including physical punishment, which can exacerbate anger and oppositionality in the child. Other important family-level influences include impaired parent–child attachment, child maltreatment (physical and sexual abuse), exposure to marital conflict and domestic violence, family poverty and crime, and family genetic liability (family histories of the disorders in this class as well as substance use, depressive, bipolar, schizophrenic, somatization, and personality disorders, as well as ADHD, have all been shown to be associated with the development of behavior disorders).

Peer-level influence on the development of behavior problems include peer rejection in childhood and antisocial peer groups, while neighborhood influences include social processes such as collective efficacy and social control.

**PREVENTION**

A number of studies have assessed the efficacy of programs targeted at the prevention of problem behaviors in children. One of the best researched programs is Fast Track ([http://fasttrackproject.org](http://fasttrackproject.org)), which is a multicomponent school-based intervention comprising a classroom curriculum targeted at conflict resolution and interpersonal skills, parent training, and interventions targeted at the school environment. Implemented in 1st through 10th grade, outcomes at grade 12 demonstrated that intervention decreased the lifetime prevalence of CD, ODD, and ADHD, but only among those at highest initial risk. Another well-researched program, the Seattle Social Development Project ([http://ssdp-tip.org/SSDP/index.html](http://ssdp-tip.org/SSDP/index.html)), also is a multicomponent school-based intervention made up of teacher, parent, and student components targeting classroom management, interpersonal problem-solving skills, child behavior management skills, and academic support skills. Implemented in 1st through 6th grades, outcomes at age 18 yr demonstrated that the intervention decreased school misbehavior and disciplinary actions and violent delinquent acts, as well as demonstrating other favorable academic and behavioral outcomes.

**SCREENING/CASE FINDING**

The parents of children presenting in the primary care setting should be queried about angry mood or aggressive, defiant, or antisocial behavior as part of the routine clinical interview. A typical screening question would be “Does [name] have a lot of trouble controlling [his/her] anger or behavior?” A number of standardized broad-band screening instruments widely used in the primary care setting (Pediatric Symptom Checklist, Strengths and Difficulties Questionnaire, Vanderbilt ADHD Diagnostic Rating Scales) have items specific to angry mood and/or aggressive behavior, and as such can be used to focus the interview.

**Stepped Management**

Because of the high rates of response to brief interventions, including bibliotherapy (use of books and other printed material to address emotional or behavioral issues with or without psychotherapy) and other media interventions, clinical practice guidelines increasingly are advocating a stepped approach to the management of youth with behavior problems. The stepped approach involves active case finding and initial management in the primary care setting if appropriate, with referral to increasingly intensive and specialized interventions as indicated by the clinical status of the patient.

**Early Intervention**

Youth and/or their parents presenting in the primary care setting who self-report or respond affirmatively to queries about difficulties managing angry mood or aggressive or antisocial behavior should be afforded the opportunity to talk about the situation with the pediatric practitioner (in private with the older youth as indicated). By engaging in active listening (e.g., “I hear how you have been feeling. Tell me more about what happened to make you feel that way”), the pediatric practitioner can begin to assess the onset, duration, context, and severity of the symptoms, and associated dangerousness, distress, and functional impairment. In the absence of acute dangerousness (e.g., homicidality, assaultiveness, psychosis, substance abuse) and significant distress or functional impairment, the pediatric practitioner can schedule a follow-up appointment within 1-2 wk to conduct a behavior assessment. At this follow-up visit, to assist with decision making around appropriate level of care, a behavior screening instrument can be administered (Table 29-4) and additional risk factors (see “Etiology/Risk Factors” above) can be explored.

For mild symptoms (manageable by the parent and not functionally impairing) and in the absence of major risk factors (homicidality, assaultiveness, psychosis, substance use, child maltreatment, parental psychopathology, or severe family dysfunction), guided self-help (anticipatory guidance) with watchful waiting may suffice. Guided self-help can include provision of educational materials (pamphlets, books, DVDs, workbooks, Internet sites) that provide information to the youth about dealing with anger-provoking situations, and advice to parents about strengthening the parent–child relationship, effective parenting strategies, and the effects of adverse environmental exposures on the development of behavior problems. An example of a self-help program for parents is the Positive Parenting Program ([Triple P; www.triplep.net](http://www.triplep.net)), self-directed version, in which parents are provided with a workbook outlining a 10 wk self-guided program that includes readings and homework tasks. In a Cochrane review, media-based parenting interventions were found to have a moderate, if variable, effect on child behavior problems. If the problematic behavior is occurring predominantly at school, the parent can be advised about the role of a special education evaluation in the assessment and management of the child's misbehavior, including the development of a behavioral intervention plan. During the period of guided self-help, follow-up visits should be scheduled.

If a mental health clinician has been colocated or integrated into the primary care setting, all parents of young children (universal prevention) as well as the parents of youth with behavior problems (indicated prevention) can be provided with a brief version of parent training. For example, Incredible Years has a 6-8 session universal prevention version designed for the parents of 2-6 yr old children, and the Triple P program has a universal prevention communications system (print and electronic media) for the parents of youth from birth to the teenage years. For children with behavior problems, the Triple P program has seminars (three 90 min sessions), brief (15-30 min consultations), and primary care (four 20-30 min consultations) versions for the parents.

<table>
<thead>
<tr>
<th>NAME OF INSTRUMENT</th>
<th>INFORMANT(S)</th>
<th>AGE RANGE</th>
<th>NUMBER OF ITEMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children's Aggression Scale</td>
<td>Parent, Teacher</td>
<td>5-18 yr</td>
<td>33 (P), 23 (T)</td>
</tr>
<tr>
<td>Eyberg Child Behavior Inventory</td>
<td>Parent</td>
<td>2-16 yr</td>
<td>36</td>
</tr>
<tr>
<td>Outburst Monitoring Scale</td>
<td>Parent</td>
<td>12-17 yr</td>
<td>20</td>
</tr>
<tr>
<td>Sutter-Eyberg Student Behavior Inventory–Revised</td>
<td>Teacher</td>
<td>2-16 yr</td>
<td>38</td>
</tr>
</tbody>
</table>
sessions in duration, focus on some combination of the following components: emotion awareness, perspective taking, anger management, social problem solving, and goal settings. Among the programs with effect sizes exceeding 0.20 include Coping Power and Problem-Solving Skills Training.

Multicomponent treatments for serious behavior disorders (such as CD) that target the broader social context include Multidimensional Treatment Foster Care and Multisystemic Therapy. Multidimensional Treatment Foster Care, delivered in a foster care setting for 6-9 mo, typically includes foster parent training and support; family therapy for biologic parents; youth anger management, social skills, and problem-solving training; school-based behavioral interventions and academic support; and psychiatric consultation and medication management, when needed. Multisystemic Therapy, typically lasting 3-5 mo, generally includes social competence training, parent and family skills training, medications, academic engagement and skills building, school interventions and peer mediation, mentoring and after-school programs, and involvement of child-serving agencies. These multicomponent programs have been designated probably efficacious because of the limited rigorous supporting evidence. Predictors of nonresponse to multicomponent treatments have included higher frequency of rule-breaking behavior and predatory aggression, higher psychopathy scores, and comorbid mood disorders.

Two classes of medication, stimulants and atypical antipsychotics, have strong evidence for the management of impulsive, anger-driven aggressive behavior, although neither are FDA approved for this indication. Resource limitations may necessitate provision of pharmacotherapy in the primary care setting; the safety and efficacy of this practice can be enhanced by regular consultation with a child and adolescent psychiatrist.

In a meta-analysis of pharmacologic treatments for aggression in youth, stimulants had a pooled mean effect size of 0.78. In a systematic review of placebo-controlled efficacy of stimulants for rating-scale assessed aggression, stimulants had a pooled effect size of 0.6 and a number needed to treat of 4. The doses of stimulants used for aggression are similar to those used for ADHD (average dose for methylphenidate: approximately 1 mg/kg/day).

Stimulants have been well-tolerated by children and adolescents, and all formulations have similar adverse event profiles. The most common (generally dose-dependent) side effects include headache, stomachache, appetite suppression, weight loss, blood pressure and heart rate increases, and delayed sleep onset. Rare side effects include irritability (particularly in younger children) and hallucinations. The cardiac effects of stimulants have been extensively studied, the most recent of which has demonstrated a hazard ratio for serious cardiovascular events of 0.75. Stimulants should be avoided in the presence of structural cardiac abnormalities and patient symptoms (syncope, palpitations, arrhythmias), or family history (e.g., unexplained sudden death) suggestive of cardiovascular disease, without cardiology consultation.

In studies of risperidone in youth with aggressive behavior, the mean effect size for aggression was 0.72. For maintenance treatment, mean effect size was 0.40. The usual daily dose of risperidone for aggression has been suggested to be 1.5-2 mg for children and 2-4 mg for adolescents. The initial starting doses have been suggested to be 0.25 mg for children and 0.5 mg for adolescents, titrating upward to the usual daily dose as indicated and tolerated.

Side effects of antipsychotic medications include sedation, extrapyramidal side effects, withdrawal dyskinesia, hyperprolactinemia, elevated liver transaminases, weight gain, cardiovascular effects, and metabolic abnormalities (elevated glucose and lipids). Ziprasidone is associated with the lowest weight gain followed by aripiprazole, ziprasidone, risperidone, and olanzapine. However, ziprasidone has not been recommended for use in children and adolescents due to lack of efficacy data. The excessive weight gain associated with olanzapine precludes its choice as a 1st-line agent.

The side effects of antipsychotic medications warrant close monitoring; abnormal movements should be monitored periodically using a standardized methodology (such as the Abnormal Voluntary
Movement Scale [AIMS checklist]; blood pressure, body mass index and fasting glucose and lipids should be checked at baseline and at regular intervals thereafter, according to standard guidelines. Consideration of weight management interventions and increased monitoring of blood glucose and lipid levels should be implemented if weight gain exceeds 90th percentile body mass index for age, or a change of 5 body mass index units occurs in youths who were obese at the beginning of treatment. In patients with a personal or family history of cardiac abnormalities, including syncope, palpitations, arrhythmias, or sudden unexplained death, a baseline electrocardiogram with subsequent monitoring should be considered, along with cardiology consultation. Alternative pharmacology should be considered if the resting heart rate exceeds 130 beats/min, or the PR, QRS, and QTc exceed 200, 120, and 460 msec, respectively.

Medication trials should be systematic, and the duration of trials should be sufficient (generally 6-8 wk) to determine the agent's effectiveness. The immediate goal of treatment is to achieve at least a 50% reduction in aggressive symptoms as assessed by a standardized rating scale (see Table 29-4). A second medication of the same class can be considered if there is insufficient evidence of response to the maximal tolerated dose by 8 wk. Care should be taken to avoid unnecessary polypharmacy, in part by discontinuing agents that have not demonstrated significant benefit. Discontinuation of the medication should be considered after a symptom-free interval.

LEVEL OF CARE

Most children and adolescents with a behavior disorder can be safely and effectively treated in the outpatient setting. Youths with intractable CD may benefit from residential or specialized foster care treatment, where more intensive treatments can be provided.

Bibliography is available at Expert Consult.

29.1 Age-Specific Behavioral Disturbances

Lovern R. Moseley, Heather J. Walter, and David R. DeMaso

INFANCY AND TODDLERHOOD

Temper tantrums and breath-holding spells are common during the first years of life and are age-typical expressions of frustration or anger. Parents who respond to toddler defiance with punitive anger can reinforce oppositional behavior. Parents are best advised to attempt to avert defiance by giving the child choices; once the child has begun a tantrum, the child can be given a timeout. It is useful to advise parents to tell their child, once he or she is calm, that the reasons for frustration are understandable, but that defiance is not acceptable.

Parents are occasionally concerned about breath-holding spells. Although some children hold their breath until they lose consciousness, sometimes leading to a brief seizure, there is no increased risk of seizure disorders in children who have had a seizure during a breath-holding spell. Parents are best advised to ignore breath holding once it has started. Without sufficient reinforcement, breath holding generally disappears.

Subtypes of breath holding spells include cyanotic, pallid, or mixed episodes. Cyanotic are the dominant type and may include a brief loss of consciousness and a very brief tonic-clonic seizure. Pallid spells may be similar to vasovagal related syncopal events in older children and initiated from similar stimuli (see Chapter 69). Iron deficiency with or without anemia may be present and some children with breath-holding spells respond to iron therapy. Medical conditions to consider should include seizures, Chiari crisis, dysautonomia, cardiac arrhythmias, and central nervous system lesions.

The first key to the office management of temper tantrums and breath-holding spells is to help parents to intercede before the child is highly distressed. The pediatrician should advise parents to intercede early in defiant behavior by calmly placing the child in timeout for a period of time approximating 1 min for each year of age. When breath holding does not respond to the parent's coaching or is accompanied by head banging or high levels of aggression, referral for a mental health evaluation is indicated.

If behavioral measures such as timeout fail, pediatricians must assess how the parents handle anger before making further recommendations about how to approach the child. Children can be frightened by the intensity of their own angry feelings and by angry feelings they arouse in their parents. Parents should model the anger control that they wish their children to exhibit. Some parents are unable to see that they lose control themselves; their own angry behavior does not help their children to internalize controls. Advising parents to calmly provide simple choices will help the child to feel more in control and to develop a sense of autonomy. Providing the child with options also typically helps reduce the child's feelings of anger and shame, which can later have adverse effects on social and emotional development.

Lying can be used by 2-4 yr olds as a method of playing with the language. By observing the reactions of parents, preschoolers learn about expectations for honesty in communication. Lying can also be a form of fantasy for children, who describe things as they wish them to be rather than as they are. To avoid an unpleasant confrontation, a child who has not done something that a parent wanted may say that it has been done. The child's sense of time and reason does not permit the realization that this only postpones a confrontation.

CHILDHOOD AND ADOLESCENCE

Lying

In school-age children, lying is generally an effort to cover up something that the child does not want to accept in his or her own behavior. The lie is invented to achieve a temporary good feeling and to protect the child against a loss of self-esteem. Habitual lying also can be promoted by poor adult modeling. Many adolescents lie to avoid adults' disapproval; lying may be used as a method of rebellion. Chronic lying can occur in combination with several other antisocial behaviors and is a sign of underlying psychopathology or family dysfunction.

Regardless of age or developmental level, when lying becomes a common way of managing conflict, intervention is warranted. Initially, the parents should confront the child to give a clear message of what is acceptable. Sensitivity and support combined with limit-setting are necessary for a successful intervention. If this behavior cannot be resolved through the parents' understanding of the situation and the child's understanding that lying is not a reasonable alternative, a mental health evaluation is indicated.

Stealing

Many children steal something at some point in their lives. When preschoolers and school-age children steal more than once or twice, the behavior may be a response to stressful environmental circumstances. Stealing can be an expression of anger or revenge for perceived frustrations with parents. In some instances, stealing becomes 1 way the child or adolescent can manipulate and attempt to control the child's or adolescent's world. Stealing also can be learned from adults.

It is important for parents to help the child undo the theft by returning the stolen articles or by rendering their equivalent either in money that the child can earn or in services. When stealing is part of a pattern of conduct problems, referral for a mental health evaluation is warranted.

Truancy and Running Away

Truancy and running away are never developmentally appropriate. Truancy may represent disorganization within the home, caretaking needs of younger siblings, developing conduct problems, or emotional problems including depression or anxiety. Whereas younger children may threaten to run away out of frustration or a desire to get back at parents, older children who run away are almost always expressing a serious underlying problem within themselves or their family, including violence, abuse, and neglect. Adolescent runaways are at high risk for substance abuse, unsafe sexual activity, and other risk-taking behaviors. Youth exhibiting truancy or running away should be referred for a mental health evaluation.
Bibliography


Fire Setting
Although interest in fire is common in early childhood, unsupervised fire setting is always inappropriate because of its extreme dangerousness. School-age children may set fires accidentally, or because of curiosity or latent hostility. These young children usually set fires by themselves within their homes. In adolescence, fire setting can be a sign of delinquency or a signal of traumatic experiences. Fire setting always requires intervention by a mental health clinician. A thorough mental health evaluation is necessary to plan the components of a successful treatment program.

Aggression and Bullying
See also Chapter 39.1.

Aggression and bullying are serious symptoms and are associated with significant morbidity and mortality. Children might not grow out of this behavior; early intervention is indicated for persistent aggressive behavior. Aggressive tendencies are heritable, although environmental factors can promote aggression in susceptible children. Both enduring and temporary stressors affecting a family can increase aggressive behavior in children. Aggression in childhood is correlated with a chaotic and impoverished family home that could be the result of chronic unemployment, family discord, exposure to community and domestic violence, criminality and psychiatric disorders as well as births to teenage mothers and those with limited resources and support. Boys are almost universally reported to be more aggressive than girls. A difficult temperament and later aggressiveness are related, although there is evidence that these children elicit punitive caregiving within the family environment, setting up a cycle of increasing aggression. Aggressive children often misperceive social cues and react with inappropriate hostility toward peers and parents.

Clinically, it is important to differentiate the causes and motives for childhood aggression. Intentional aggression may be primarily instrumental, to achieve an end, primarily hostile, to inflict physical or psychologic pain, or primarily angry and impulsive. Children who are callous and not empathetic and who are often aggressive require mental health intervention. These children are at high risk for suspension from school and eventual school failure. Learning disorders are common, and aggressive children should be screened. Other forms of psychopathology may be present; in particular, aggressive children might have ADHD, ODD, IED, CD, and/or disruptive mood dysregulation disorder.

Aggressive behavior in boys is relatively consistent from the preschool period through adolescence; a boy with a high level of aggressive behavior at 3-6 yr of age has a high probability of carrying this behavior into adolescence, especially without effective intervention. The developmental progression of aggression among girls is less-well studied. There are fewer girls with physically aggressive behavior in early childhood; interpersonal coercive behavior, especially in peer relationships, is not uncommon among girls and may be related to the development of more physical aggression in adolescence (fighting, stealing).

Children exposed to aggressive models on television, in video games, or in play show more aggressive behavior compared with children not exposed to these models. Parents’ anger and aggressive or harsh punishment model behavior that children might imitate when they are physically or psychologically hurt. Parents’ abuse may be transmitted to the next generation by several modes: children imitate aggression that they have witnessed, abuse can cause brain injury (which itself predisposes the child to violence), and internalized rage often results from abuse.

Cutting and Other Self-Injurious Behaviors
Cutting and other self-injurious behaviors have been occurring in increased rates among children as young as age 11 yr through adolescence. Rates are higher in girls than boys, but cutting and other self-injurious behaviors do occur in both. The behavior involves the deliberate carving, cutting, scratching, or burning of the skin with fingernails or other objects sharp enough to cause injury (razors, scissors, broken glass, hard plastic, knives, staples, fire). Oftentimes the behavior does not occur with the intention of suicide but can be associated with it and can unintentionally result in significant harm or even death. Youth often report that they have friends who “cut” and have reported that it is a way to feel better and so they have tried it as well. There is increased access to message boards and websites on the internet where youth have shared their stories of self-injury; these postings may have contributed to experimentation. The behavior is usually triggered by psychological distress and is also correlated with depression, anxiety, peer victimization, low self-esteem, substance abuse, eating disorders, impulsivity, delinquency, and neglectful or highly punitive parenting practices, as well as a history of physical or sexual abuse. Parents should be advised to monitor their children's media access and be aware of their peer group. Learning that their child has been engaging in this behavior can be very frightening for parents as they are unsure of what to do or the reasons why their child is engaging in this behavior. It is imperative that they seek mental healthcare for their child.

Bibliography is available at Expert Consult.
Bibliography

The essential features of autism spectrum disorder (ASD) are persistent impairment in reciprocal social communication and interaction, and restricted, repetitive patterns of behavior or interests (Table 30-1). ASD encompasses disorders previously referred to as early infantile autism, childhood autism, Kanner autism, high functioning autism, atypical autism, Asperger disorder, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified. These specific diagnoses are not reliably distinguishable or consistently applied across different treatment centers. Individuals diagnosed with one of these previous diagnoses should be given the diagnosis of ASD.

**DESCRIPTION**

**Social Communication and Interaction Deficits**

Aberrant development of social communication and impaired ability to engage in reciprocal social interactions are hallmark symptoms of ASD. Deficits in social–emotional reciprocity (the ability to engage with others and share thoughts and feelings) are evident early in children with ASD who show little or no initiation of social interaction and little or no sharing of emotions or imitative behaviors. Children may present with abnormal social approach, failure of back-and-forth conversation, and difficulties processing and responding to complex social cues. Infants <6 mo of age may or may not demonstrate features typical of ASD.

Impairments in nonverbal social communication are manifested by absent, reduced, or atypical use of eye contact, gestures, facial expressions, body orientation, or speech intonation. Youth may fail to smile, orient to name, or use gestures to point or show. Abnormal eye contact with failure to follow someone’s pointing or eye gaze is characteristic. In patients with fluent language, poorly integrated verbal and nonverbal communication may result in odd, wooden, or exaggerated body language during social interactions (Table 30-2).

Children with ASD may demonstrate absent, reduced, or atypical social interest, manifested by rejection of others, passivity, or inappropriate approaches that seem aggressive and disruptive. In young children, lack of shared, age-appropriate flexible pretend and symbolic play is seen, with children often persistent on playing by very fixed rules.
Autism behaviors. Within these 2 categories, severity is rated levels 1-3, with both deficits in social communication and in restricted, repetitive behavior.

The severity of ASD is based on evaluations of impairment caused by deficits in social communication and in restricted, repetitive behaviors. Within these 2 categories, severity is rated levels 1-3, with level 3 implying most severe deficit with a need for the most substantial support (Table 30-3).

### Specifiers/Associated Features

ASD is specified as occurring with or without accompanying intellectual and language impairment, and associated with a known medical or genetic condition, environmental factor, or other neurodevelopmental, mental, or behavioral disorder. Children with ASD vary in their verbal abilities. Language level in individuals with ASD “without accompanying language impairment” may speak in full sentences or have fluent speech. ASD specified “with accompanying language impairment” can range from nonverbal speech to single word or phrase speech (capable of imitating songs, rhymes, or television commercials). Receptive language may lag behind expressive language development in ASD. Early abnormal language concerns include absent babbling or gestures by 12 mo, absent single words by 16 mo, and absent 2-word purposeful phrases by 24 mo, as well as any loss of language or social skills at any time. Language, if present, is often one-sided, lacking social reciprocity, idiosyncratic, repetitive, and used to request or label rather than comment, share feelings, or converse.

Intellectual functioning can vary from intellectual impairment (intellectual developmental disorder) to superior intellectual functioning in select areas (splinter skills, savant behavior) (“with or without accompanying intellectual impairment”). Some children show typical development in certain skills and can even show areas of strength in specific areas (puzzles, art, or music). The intellectual profile of an individual may be uneven, with gaps in verbal and nonverbal learning ability and intellectual and adaptive functional skills.

Motor deficits, including odd gait, clumsiness, dyspraxia, and other abnormal motor signs (e.g., walking on tiptoes) are often present. Stereotypic movement or tic disorders may go unnoticed given aforementioned restricted behavioral patterns. Self-injury (head banging, biting the wrist) may occur. Some youth develop catatonic-like motor behavior (slowing and “freezing” mid-action) though most do not go onto develop a full episode with mutism, posturing, grimacing, and waxy flexibility.

Epilepsy is a common comorbidity, and any type of seizure may be observed in ASD. Epilepsy is associated with greater intellectual disability and lower verbal ability. Mutations in the *BCKD-kinase* gene is a syndrome associated with autism, epilepsy and intellectual disability. Youth with ASD are also prone to anxiety and depression as well as abnormalities in attention and hyperactivity.

Language, social, or a mixed pattern of regression may occur in the first 1-2 years. In some, a diagnosis of Landau Kleffner syndrome is identified; in others regression may be due to the onset of epilepsy or abnormal EEG findings in the absence of clinical seizures. Levetiracetam also causes a reversible autistic regression syndrome.

### EPIDEMIOLOGY

The Centers for Disease Control and Prevention estimates the prevalence of ASD in the United States as 11.3/1,000 (prior estimated prevalence range: 0.7/10,000 to 72.6/10,000 across 36 earlier surveys). Recent higher reported rates of the disorder appear to be related to differences in diagnostic criteria and practices, inclusion of subthreshold cases, age of children screened, and location of the study. The male:female ratio is estimated to be 4:1. The incidence of ASD may be higher in immigrant populations.

### ETIOLOGY/RISK FACTORS

#### Genetic and Familial Factors

There is a high recurrence risk (2-19%) for ASD among siblings, as well as a higher concordance rate (37-90%) in twin studies. Closer spacing of pregnancies, advanced maternal or paternal age, and extremely premature birth (<26 wk gestational age) as well as family members with learning problems, psychiatric disorders, and social disability, have been identified as risk factors. Multiple genes are viewed as involved in autism with studies supporting a role for both common (>5% of general population) and rare genetic variations contributing to the disorder. For example, Timothy syndrome, characterized by

### Table 30-1: DSM-5 Diagnostic Criteria for Autism Spectrum Disorder

<table>
<thead>
<tr>
<th>A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history:</th>
<th>B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Deficits in social-emotional reciprocity.</td>
<td>1. Stereotyped or repetitive motor movements, use of objects, or speech.</td>
</tr>
<tr>
<td>2. Deficits in nonverbal communicative behaviors used for social interaction.</td>
<td>2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior.</td>
</tr>
<tr>
<td>3. Deficits in developing, maintaining, and understanding relationships.</td>
<td>3. Highly restricted, fixated interests that are abnormal in intensity or focus.</td>
</tr>
<tr>
<td>C. Symptoms must be present in the early developmental period (may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).</td>
<td>4. Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment.</td>
</tr>
<tr>
<td>D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.</td>
<td>5. Persistent deficits in social-emotional reciprocity.</td>
</tr>
<tr>
<td>E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay.</td>
<td>Deficits in nonverbal communicative behaviors used for social interaction.</td>
</tr>
</tbody>
</table>

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013) American Psychiatric Association, pp. 50–51. 

Children with ASD may prefer solitary activities and interactions with much younger or older people. A desire to establish friendships without complete understanding of the components of friendship (one-sided friendships based solely on shared special interests) can be seen in some children, while an absence of interest in peers may be seen in others. Some youth show deficits in empathy and understanding what another person might be thinking.

#### Restricted and Repetitive Patterns

The second core characteristic of ASD is restricted, repetitive patterns of behavior, interests, or activities. These include stereotyped movements (hand flapping, finger flapping), repetitive use of objects (spinning coins, lining up toys), repetitive and abnormal speech (echolalia [delayed or immediate parroting of heard words], pronoun reversal, nonsense rhyming, idiosyncratic phrases); insistence on sameness and inflexible adherence to routines or ritualized patterns of behavior (distress at small changes, insistence on adherence to rules, rituals and routines, rigid thinking, repetitive questioning); highly restricted and fixated interests of abnormal intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests); and hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment (e.g., extreme responses to specific sounds or textures, excessive smelling or touching of objects, fascination with lights or spinning objects, apparent indifference to pain, heat, or cold) (see Table 30-2).

The symptoms of ASD must be present in the early developmental period, must cause clinically significant functional impairment, and must not be better explained by intellectual disability or global developmental delay.

#### Severity

The severity of ASD is based on evaluations of impairment caused by both deficits in social communication and in restricted, repetitive behaviors. Within these 2 categories, severity is rated levels 1-3, with...

**Table 30-2** Signs and Symptoms of Possible Autism in Preschool Children (or Equivalent Mental Age)

<table>
<thead>
<tr>
<th>Social interaction and reciprocal communication behaviors</th>
<th>Eye contact, pointing, and other gestures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spoken language</strong></td>
<td>• Reduced or absent use of gestures and facial expressions to communicate (although may place an adult's hand on objects)</td>
</tr>
<tr>
<td>• Language delay (in babble or words—for example, using fewer than 10 words by the age of 2 yr)</td>
<td>• Reduced and poorly integrated gestures, facial expressions, body orientation, eye contact (looking at people's eyes when speaking), and speech used in social communication</td>
</tr>
<tr>
<td>• Regression in or loss of use of speech</td>
<td>• Reduced or absent social use of eye contact (assuming adequate vision)</td>
</tr>
<tr>
<td>• Spoken language (if present) may include unusual features, such as: vocalizations that are not speech-like; odd or flat intonation; frequent repetition of set words and phrases (echolalia); reference to self by name or “you” or “she” or “he” beyond age 3 yr</td>
<td>• Reduced or absent “joint attention” (when 1 person alerts another to something by means of gazing, finger pointing, or other verbal or nonverbal indication for the purpose of sharing interest). This would be evident in the child from lack of: ○ Gaze switching ○ Following a point (looking where the other person points to—may look at hand) ○ Using pointing at or showing objects to share interest</td>
</tr>
<tr>
<td>• Reduced and/or infrequent use of language for communication—for example, use of single words, although able to speak in sentences</td>
<td><strong>Ideas and imagination</strong></td>
</tr>
<tr>
<td><strong>Responding to others</strong></td>
<td>• Reduced or absent imagination and variety of pretend play</td>
</tr>
<tr>
<td>• Absent or delayed response to name being called, despite normal hearing</td>
<td><strong>Unusual or restricted interests and/or rigid and repetitive behaviors</strong></td>
</tr>
<tr>
<td>• Reduced or absent responsive social smiling</td>
<td>• Repetitive &quot;stereotypical&quot; movements such as hand flapping; body rocking while standing; spinning; finger flicking</td>
</tr>
<tr>
<td>• Reduced or absent responsiveness to other people's facial expressions or feelings</td>
<td>• Repetitive or stereotyped play—for example, opening and closing doors</td>
</tr>
<tr>
<td>• Unusually negative response to the requests of others (“demand avoidance” behavior)</td>
<td>• Over focused or unusual interests</td>
</tr>
<tr>
<td>• Rejection of cuddles initiated by parent or carer, although the child himself or herself may initiate cuddles</td>
<td>• Excessive insistence on following own agenda</td>
</tr>
<tr>
<td><strong>Interacting with others</strong></td>
<td>• Extremes of emotional reactivity to change or new situations; insistence on things being “the same”</td>
</tr>
<tr>
<td>• Reduced or absent awareness of personal space</td>
<td>• Over-reaction or under-reaction to sensory stimuli, such as textures, sounds, smells</td>
</tr>
<tr>
<td>• Reduced or absent social interest in others, including children of his or her own age—may reject others; if interested in others, he or she may approach others inappropriately, seeming to be aggressive or disruptive</td>
<td>• Excessive reaction to the taste, smell, texture, or appearance of food, or having extreme food fads</td>
</tr>
<tr>
<td>• Reduced or absent imitation of others’ actions</td>
<td><strong>Unusual or restricted interests and/or rigid and repetitive behaviors</strong></td>
</tr>
<tr>
<td>• Reduced or absent initiation of social play with others, plays alone</td>
<td>• Repetitive &quot;stereotypical&quot; movements such as hand flapping; body rocking while standing; spinning; finger flicking</td>
</tr>
<tr>
<td>• Reduced or absent enjoyment of situations that most children like—for example, birthday parties</td>
<td>• Repetitive or stereotyped play—for example, opening and closing doors</td>
</tr>
<tr>
<td>• Reduced or absent sharing of enjoyment</td>
<td>• Over focused or unusual interests</td>
</tr>
</tbody>
</table>

From the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 52
Neurobiologic Factors
The high rates of seizure disorder suggest a role for neurobiologic factors in ASD. The number of different areas of the brain affected by autism suggests a diverse and widely distributed set of affected neural systems. Postmortem studies reveal various abnormalities, particularly within the limbic system. Structural MRI reveals an overall increase of brain size, and diffusion tensor imaging studies suggest aberrations in white matter tract development. Functional MRI identifies difficulties in tasks involving social and affective judgments and differences in the processing of face and nonface stimuli. Poor neuronal connectivity in various brain regions also is reported. Elevated peripheral levels of serotonin are a replicated neurochemical finding of unclear significance. A role for dopamine is suggested given the problems with overactivity and stereotyped mannerisms and the positive response of such behaviors to antipsychotic medications.

Neuropsychological correlates of ASD include impairments in executive functioning (e.g., simultaneously engaging in multiple tasks), weak central coherence (integrating information into meaningful wholes), and deficits in theory of mind tasks (taking the perspective of another person). The empathizing-systemizing personality theory describes the autistic mind in terms of impaired empathy alongside intact or even superior systemizing (the drive to analyze or construct systems).

Environmental exposures early in the 1st trimester of pregnancy that have been linked to ASD in epidemiologic studies include thalidomide, misoprostol, rubella infection, valproic acid, and the organophosphate insecticide chlorpyrifos. Prenatal folic acid supplementation may reduce the risk of ASD. There has been concern about vaccines as a postnatal environmental cause for ASD. The focus has been on either the measles-mumps-rubella vaccine or the thimerosal preservative as a causative factor. All available data have not supported either hypothesis.

Neuropathology Factors
The head circumference in ASD is normal or slightly smaller than normal at birth until 2 mo of age. Afterward, children with ASD show an abnormally rapid increase in head circumference from 6-14 mo of age, increased brain volume in 2-4 yr olds, increased volume of the cerebellum, cerebrum, and amygdala, and marked abnormal growth in the frontal, temporal, cerebellar, and limbic regions of the brain. Early, accelerated brain growth during the first several years of life is followed by abnormally slow or arrested growth, resulting in areas of underdeveloped and abnormal circuitry in parts of the brain. Areas of the brain responsible for higher-order cognitive, language, emotional, and social functions are most affected.

CLINICAL COURSE
ASD symptoms are typically recognized during the 2nd yr of life but can be seen earlier than 12 mo if developmental delays are severe. Initial symptoms most frequently involve delayed language accompanied by lack of social interest or odd play patterns. During the 2nd yr, odd and repetitive behaviors and the absence of typical play become more apparent. It is typical for parents to report that there was no period of normal development or that there was a history of unusual behaviors. Less commonly (in 20-40% of cases), a period of apparently normal development is reported before a loss of skills. In adolescence, a small number of individuals with ASD make marked developmental gains; another subgroup will deteriorate (self-injury, aggression).

DIFFERENTIAL DIAGNOSIS
ASD must be differentiated from communication disorders (especially social communication disorder), intellectual disability (see Chapter 36), sensory impairments (especially deafness), reactive attachment disorder, obsessive-compulsive and related disorders, anxiety disorders (see Chapter 25) including selective mutism, schizophrenia (see Chapter 31), stereotypic movement disorder (see Chapter 24.2), attention-deficit/hyperactivity disorder (ADHD), and Rett syndrome (see Chapter 599).

Autistic-like behavior has been noted in many metabolic syndrome and genetic disorders. These include adenylsuccinate lyase deficiency, PKU, glucose-6-phosphatase deficiency, adenosine deaminase deficiency, succinic semialdehyde dehydrogenase deficiency, disorders of creatine transport and metabolism, propionic acidaemia, MELAS and other mitochondrial disorders, Danon disease, tuberous sclerosis, fragile X syndrome, Smith Lemli Opitz syndrome, myotonic dystrophy, dystrophinopathies, Cohen and Myhre syndromes, muscle-eye-brain disease, and various genetic microdeletions or duplications, including deletion 22q11.2.

Developmental language disorders and intellectual disability have an impact on socialization and may be mistaken for ASD. The distinction is particularly difficult in preschool children. When an individual shows impairment in social communication and social interactions but without abnormal nonverbal communication or restricted, repetitive patterns of behavior, a diagnosis of social communication disorder should be considered. If there is no apparent discrepancy between the level of social-communicative skills and other intellectual skills, a diagnosis of intellectual disability should be considered.

Children with reactive attachment disorder (typically occurring in the face of emotional neglect; see Chapter 40) may exhibit deficits in attachment and therefore inappropriate social responsivity, but these usually improve substantially if adequate caretaking is provided. Obsessive-compulsive disorder (see Chapter 25) has a later onset than ASD, is not typically associated with social and communicative impairments, and is characterized by repetitive patterns of behavior that are ego dystonic. Symptoms that characterize anxiety disorders, such as excessive worry, the need for reassurance, the inability to relax, and feelings of self-consciousness are also seen in ASD, particularly among higher functioning individuals. However, the 2 conditions can be differentiated by the prominent social and communicative impairments seen in ASD but not anxiety disorders, and the developed social insight of children with anxiety disorders, which is not seen in ASD. Differentiating childhood schizophrenia from autism can be difficult, as both are characterized by social impairments and odd patterns of thinking; florid delusions and hallucinations are rarely seen in autism.

Motor stereotypes are among the diagnostic criteria for ASD, so an additional diagnosis of stereotypic movement disorder should not be given if the movements are better explained by ASD. However when stereotypes cause self-injury and become a focus of treatment, both diagnoses may be appropriate. Similarly, an additional diagnosis of ADHD should only be given when attentional difficulties or hyperactivity exceed those typically observed in children of comparable mental age.

During the regressive phase of Rett syndrome (ages 1-4 yr), disruptive social interaction may be observed and affected children may meet diagnostic criteria for ASD. After this phase, social communication improves and an additional diagnosis of ASD should be considered only if all criteria for ASD are met.

COMORBIDITIES
Given difficulties in communication (mutism) and cognitive impairment, issues of comorbidity in ASD can be quite complex. The process of diagnostic overshadowing (the tendency to fail to diagnose other comorbid conditions when a more noticeable condition is present) may occur. Most studies do show increased rates of anxiety and attentional disorders.

In most epidemiologically based samples of persons with autistic disorder, approximately 50% exhibit severe or profound intellectual disability, 35% exhibit mild to moderate intellectual disability, and the remaining 20% have IQs in the normal range. Verbal skills are typically more impaired than nonverbal skills. Intellectual impairment is not an essential diagnostic feature of autism; it is necessary and important for the diagnosis of intellectual disability to be made.
Neurologic comorbidities include epilepsy, sleep dysfunction, motor delay, dyspraxia, incoordination, and gait disturbances.

A range of behavioral difficulties can be observed in ASD including hyperactivity, obsessive compulsive phenomena, self-injury, aggression, stereotypies, tics, and affective symptoms. The issue of whether these qualify as additional disorders is complex. Affective symptoms are frequently observed and include lability, inappropriate affective responses, anxiety, and depression. Impairments in emotion regulation processes can lead to under- and overreactivity. Overt clinical depression is sometimes observed, and this may be particularly true for adolescents. Case reports and case series suggest possible associations with bipolar disorders and tic disorders. Attentional difficulties (ADHD) are also frequent in autism, reflecting cognitive, language, and social problems.

**SEQUELAE**

Most persons with ASD remain within the spectrum as adults, and regardless of their intellectual functioning, continue to experience problems with independent living, employment, social relationships, and mental health. Some children, especially those with communication abilities, can grow up to live self-sufficient lives in the community with employment. Others remain dependent on their family or require placement in facilities outside the home. Because early, intensive therapy can improve language and social function, delayed diagnosis can lead to a poorer outcome. A better prognosis is associated with higher intelligence, functional speech, and less-bizarre symptoms and behavior. The symptom profile for some children might change as they grow older, and risk of seizures or self-injurious behavior becomes more common. ASD is not a degenerative disorder and it is typical for learning and compensation to continue throughout life.

**SCREENING/CASE FINDING**

All children should receive autism-specific screening at 18 and 24 mo of age, in addition to broad developmental screening at 9, 18, and 24 mo (Fig. 30-1). In some instances screening may be relevant to older children, such as those who are more intellectually able and whose

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**Figure 30-1 Surveillance and screening algorithm: autism spectrum disorders (ASDs).** (From Plauche Johnson C, Myers SM, Council on Children with Disabilities: Identification and evaluation of children with autism spectrum disorders, Pediatrics 120:1183–1215, 2007.)
1a: Pediatric patient at preventive care visit

1b: Extra visit for autism-related concern, asd risk factor, or other developmental/behavioral concern

1c: Comprehensive ASD evaluation

2: Perform surveillance

Score 1 for each risk factor:
- Sibling with ASD
- Parental concern
- Other caregiver concern
- Pediatrician concern

2 - Developmental surveillance is a flexible, longitudinal, continuous, and cumulative process whereby health care professionals identify children who may have developmental problems. There are 5 components of developmental surveillance: eliciting and attending to the parents' concerns about their child's development, documenting and maintaining a developmental history, making accurate observations of the child, identifying the risk and protective factors, and maintaining an accurate record and documenting the process and findings. The concerns of parents, other caregivers, and pediatricians all should be included in determining whether surveillance suggests that the child may be at risk of an ASD. In addition, younger siblings of children with an ASD should also be considered at risk, because they are 10 times more likely to develop symptoms of an ASD than children without a sibling with an ASD. Scoring risk factors will help determine the next steps. (Go to step 2)

3 - Scoring risk factors:
- If the child does not have a sibling with an ASD and there are no concerns from the parents, other caregivers, or pediatrician: Score = 0 (Go to step 4)
- If the child has only 1 risk factor, either a sibling with ASD or the concern of a parent, caregiver, or pediatrician: Score = 1 (Go to step 3a)
- If the child has 2 or more risk factors: Score = 2+ (Go to step 8)

3a: Is the patient at least 18 months old?

3a: If the child's age is <18 months, (Go to step 5a)

3a: If the child's age is ≥18 months, (Go to step 5b)

4 - In the absence of established risk factors and parental/provider concerns (score = 0), a level-1 ASD-specific tool should be administered at the 18- and 24-month visits. (Go to step 5c) If this is not an 18- or 24-month visit, (Go to step 7b)

Note: In the AAP policy, "Identifying Infants and Young Children With Developmental Disorders in the Medical Home: An Algorithm for Developmental Surveillance and Screening," a general developmental screen is recommended at the 9-, 18-, and 24- or 30-month visits and an ASD screening is recommended at the 18-month visit. This clinical report also recommends an ASD screening at the 24-month visit to identify children who may regress after 18 months of age.

5a: Evaluate social-communication skills

5b: Administer ASD-specific screening tool

5c: For all children ages 18 or 24 months, regardless of risk factors, the pediatrician should use an ASD-specific screening tool. (Go to step 6b)

5a: If the child's age is <18 months, the pediatrician should use a tool that specifically addresses the clinical characteristics of ASDs, such as those that target social-communication skills. (Go to step 6a)

5b: If the child's age is ≥18 months, the pediatrician should use an ASD-specific screening tool. (Go to step 6a)

5c: If the child has more than 1 risk factor, the pediatrician should use an ASD-specific screening tool. (Go to step 6b)

6a - When the result of the screening is negative, Go to step 7a

6b - When the result of the ASD screening (at 18- and 24-month visits) is negative, Go to step 7b

6a: When the result of the screening is positive, Go to step 8

6b: When the result of the ASD screening (at 18- and 24-month visits) is positive, Go to step 8

6a: Are the results positive or concerning?

6b: Are the results positive or concerning?

7a: If the child demonstrates risk but has a negative screening result, information about ASDs should be provided to parents. The pediatrician should schedule an extra visit within 1 month to address any residual ASD concerns or additional developmental/behavioral concerns after a negative screening result. The child will then re-enter the algorithm at 1b. A “wait-and-see” approach is discouraged. If the only risk factor is a sibling with an ASD, the pediatrician should maintain a higher index of suspicion and address ASD symptoms at each preventive care visit, but an early follow-up within 1 month is not necessary unless a parental concern subsequently arises.

7a: 1. Provide parental education
2. Schedule extra visit within 1 month
3. Re-enter algorithm at 1b

7b: - If this is not an 18- or 24-month visit, or when the result of the ASD screening is negative, the pediatrician can inform the parents and schedule the next routine preventive visit. The child will then re-enter the algorithm at 1a.

7b: 1. Schedule next preventive visit
2. Re-enter algorithm at 1b

8: If the screening result is positive for possible ASD in step 6a or 6b, the pediatrician should provide peer-reviewed and/or consensus-developed ASD materials. Because a positive screening result does not determine a diagnosis of ASD, the child should be referred for a comprehensive ASD evaluation, to early intervention/early childhood education services (depending on child’s age), and an audiologic evaluation. A categorical diagnosis is not needed to access intervention services. These programs often provide evaluations and other services even before a medical evaluation is complete. A referral to intervention services or school also is indicated when other developmental/behavioral concerns exist, even though the ASD screening result is negative. The child should be scheduled for a follow-up visit and will then re-enter the algorithm at 1b. All communication between the referral sources and the pediatrician should be coordinated.

8: 1. Provide parental education
2. Simultaneously refer for:
   a. Comprehensive ASD evaluation
   b. Early intervention/early childhood education services
   c. Audiologic evaluation
3. Schedule follow-up visit
4. Re-enter algorithm at 1b

AAP information for parents about ASDs includes: “Is Your One-Year-Old Communicating with You?” and “Understanding Autism Spectrum Disorders.”

*Available at www.aap.org

Figure 30-1, cont’d
social disability is therefore more likely to be detected later. A number of screening instruments for ASD have been developed that may be helpful to the pediatric practitioner. For example, the Modified Checklist for Autism in Toddlers (M-CHAT) is a free online 23-item autism screening tool designed to identify children 16-30 mo of age who should receive a more thorough assessment for possible early signs of ASD or developmental delay (https://www.m-chat.org/index.php).

**ASSESSMENT**

If screening indicates ASD symptomatology, a thorough diagnostic assessment should be performed to determine whether full criteria are met. Multidisciplinary assessment is optimal in facilitating early diagnosis, treatment, and coordinated multiagency collaboration. Evaluations from various professionals, including a developmental pediatrician or pediatric neurologist, medical geneticist, child and adolescent psychiatrist, speech-language pathologist, occupational or physical therapist, or medical social worker may be indicated. The Autism Diagnostic Observation Schedule (ADOS), which is a semistructured interactive examination by a professional trained in its administration, is the standard diagnostic tool. The use of such instruments supplements, but does not replace, informed clinical judgment.

All children with ASD should have a medical assessment, which typically includes a physical examination, a hearing screen, a Wood's lamp examination for signs of tuberous sclerosis (see Chapter 396.2), and genetic testing, which should include chromosomal microarray (CMA). In a community sample of children with ASD, diagnostic yield 0.57% for fragile X testing, and 24% for CMA. CMA is recommended by medical geneticists as the standard of care for the initial evaluation of children with ASD, but does not always detect fragile X or Rett syndromes.

Unusual features in the child (dysmorphology, staring spells) should prompt additional evaluations. The categories of potential organic etiologies includes infectious (encephalitis or meningitis), endocrinologic (hypothyroidism), metabolic (homocystinuria, phenylketonuria), traumatic (head injury), toxic (fetal alcohol syndrome), or genetic (chromosomal abnormality). Certain developmental disorders, most notably Landau-Kleffner syndrome, should be ruled out (characterized by a highly distinctive electroencephalogram abnormality and marked aphasia). Neuroimaging, electroencephalography, and additional laboratory tests should be obtained when relevant, based on examination or history (testing for the MeCP2 gene in females for possible Rett disorder). Table 30-4 summarizes potential medical tests in the assessment of ASD.

Psychological assessments that clarify cognitive ability and adaptive skills are indicated for treatment planning. Deficits in language and socialization often make it difficult to obtain an accurate estimate of a child’s intellectual potential. Some children with ASD perform adequately on nonverbal tests, and those with developed speech can show adequate intellectual capacity. Communication assessment, including measures of both receptive and expressive vocabulary as well as language use (particularly social or pragmatic), is also helpful relative to diagnosis and treatment planning. Occupational and physical therapy evaluations may be needed to evaluate sensory and/or motor difficulties. Sleep is also an important variable to assess.

**TREATMENT**

The pediatric practitioner should aim to foster a long-term collaborative relationship with the family that will vary in intensity over time. For young children, diagnosis and identification of treatment programs will generally be the major focus, whereas for school age children behavioral and medication issues will often become a priority. Vocational training along with future self-sufficiency planning becomes critical in adolescence and early adulthood. It is helpful to the family for the pediatric practitioner to maintain an active role in long-term treatment planning, providing family support, and navigating the healthcare and educational systems.

**Psychosocial Interventions**

Structured behavioral, educational, and communication interventions are effective for many children with ASD and are associated with better outcomes. Several comprehensive treatment approaches are effective for certain groups of children, although none of the approaches has clearly emerged as superior.

**Table 30-4 Medical and Genetic Evaluation of Children with Autism Spectrum Disorder**

<table>
<thead>
<tr>
<th>Recommended evaluations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Careful physical examination to identify dysmorphic physical features</td>
</tr>
<tr>
<td>Macrocephaly</td>
</tr>
<tr>
<td>Wood's lamp examination for tuberous sclerosis</td>
</tr>
<tr>
<td>Formal audiologic evaluation</td>
</tr>
<tr>
<td>Lead test; repeat periodically in children with pica</td>
</tr>
<tr>
<td>Chromosomal microarray</td>
</tr>
<tr>
<td>Consider if results of above evaluation are normal and if accompanying intellectual impairment</td>
</tr>
<tr>
<td>FISH test for region 15q11q13 to rule out duplications in Prader-Willi/Angelman syndrome</td>
</tr>
<tr>
<td>Fluorescence in situ hybridization (FISH) test for telomeric abnormalities</td>
</tr>
<tr>
<td>Test for mutations in MECP2 gene (Rett syndrome) in females</td>
</tr>
<tr>
<td>DNA testing for fragile X syndrome</td>
</tr>
<tr>
<td>Metabolic testing to consider based on clinical features (emesis, hypotonia, lethargy, ataxia, coarse facial features of a storage disease, multiple organs involved)</td>
</tr>
<tr>
<td>Fasting blood glucose</td>
</tr>
<tr>
<td>Plasma amino acids</td>
</tr>
<tr>
<td>Ammonia and lactate</td>
</tr>
<tr>
<td>Fatty acid profile, paroxysmal</td>
</tr>
<tr>
<td>Carnitine</td>
</tr>
<tr>
<td>Acylcarnitine, quantitative</td>
</tr>
<tr>
<td>Homocysteine</td>
</tr>
<tr>
<td>Urine amino acids</td>
</tr>
<tr>
<td>Urine organic acids</td>
</tr>
<tr>
<td>Urine purine/pyrimidines</td>
</tr>
<tr>
<td>Urine acylglycine, random</td>
</tr>
<tr>
<td>Plasma 7-dehydrocholesterol (Smith-Lemli-Opitz disease screening)</td>
</tr>
<tr>
<td>Medical testing to consider based on clinical features</td>
</tr>
<tr>
<td>Complete blood cell count</td>
</tr>
<tr>
<td>Liver enzymes</td>
</tr>
<tr>
<td>Biotinidase</td>
</tr>
<tr>
<td>Thyroxine, thyroid-stimulating hormone</td>
</tr>
<tr>
<td>Ceruloplasmin/serum copper</td>
</tr>
<tr>
<td>EEG if the following clinical features are noted</td>
</tr>
<tr>
<td>Clinically observable seizures</td>
</tr>
<tr>
<td>History of significant regression in social or communication functioning</td>
</tr>
</tbody>
</table>


**Applied behavioral analysis (ABA)** is a behavioral intervention that is informed by basic and empirically supported learning principles. A widely disseminated comprehensive ABA program is Early Intensive Behavioral Intervention. Early Intensive Behavioral Intervention is intensive and highly individualized with up to 40 hr per week of one-to-one direct teaching, initially using discrete trials to teach simple skills and progressing to more complex skills such as initiating verbal behavior. ABA techniques have efficacy for specific problem behaviors and to be effective when applied to academic tasks, adaptive living skills, communication, social skills, and vocational skills.

Older children and adolescents with relatively higher intelligence, but with poor social skills and psychiatric symptoms, can benefit from more intensive behavioral or cognitive-behavioral therapy and/or supportive psychotherapy. The focus is on achieving social communication competence, emotional and behavioral regulation, and functional adaptive skills necessary for independence.

Children with ASD need a structured educational approach with explicit teaching. Effective programs typically involve planned, intensive, individualized intervention with an experienced, interdisciplinary
team of providers, and family involvement to ensure generalization of skills. Two structured educational models with demonstrated efficacy include the Early Start Denver Model and the Treatment and Education of Autism and related Communication handicapped Children (TEACCH) program. The individualized educational plan (IEP) should reflect an accurate assessment of the child’s strengths and vulnerabilities with an explicit description of services to be provided, goals and objectives, and procedures for monitoring effectiveness. Development of an appropriate IEP is central in providing effective service to the child and family.

Communication is generally addressed in the child’s IEP in coordination with the speech-language pathologist. Children who do not yet use words can be helped through use of alternative communication modalities such as sign language, electronic communication boards, visual supports, picture exchange, and other forms of augmentative communication. For individuals with fluent speech, the focus should be on pragmat (social) language skills training.

There is a lack of evidence for most other forms of psychosocial intervention. Studies of sensory-oriented interventions, such as auditory integration training, sensory integration therapy, and touch therapy/massage have contained methodologic flaws and have yet to show replicable improvements. There is also limited evidence thus far for what are usually termed developmental, social-pragmatic models of intervention. Children with ASD are psychiatrically hospitalized at substantially higher rates than the non-ASD population. The efficacy of this level of care is unknown, although there is preliminary evidence for the efficacy of hospital psychiatry units that specialize in this level of care is unknown, although there is preliminary evidence for the efficacy of hospital psychiatry units that specialize in this level of care for the treatment of irritability in ASD, as evidenced by physical aggression, self-injury, and severe tantrum behavior. In youth weighing \(<20\) kg, the initial dose of risperidone is 0.25 mg/day with a target dose of 0.5 mg/day, and maximum does of 3 mg/day. In those weighing \(\geq 20\) kg, the initial dose of risperidone is 0.5 mg/day with a target dose of 1 mg/day, and maximum dose of 3 mg/day. For aripiprazole, the initial dose is 2 mg/day with a target dose of 5-10 mg/day, and maximum dose of 15 mg/day.

The atypical antipsychotic agents also reduce hyperactivity in ASD, though stimulants and atomoxetine appear to be promising for hyperactivity. There is also evidence that repetitive behaviors and stereotypies in ASD may respond to the antipsychotics. Selective serotonin reuptake inhibitors do not have evidence supporting their use for repetitive behaviors or irritability in ASD; they may have efficacy for the treatment of co-occurring depressive and anxiety disorders. The doses of these latter medications would parallel clinical prescribing practices for the specific target symptom (hyperactivity) and/or mental stabilization. There is insufficient evidence to support the use of mood stabilizers.

Combining medication with parent training appears to be moderately more efficacious than medication alone for reducing serious behavioral disturbance, and modestly more efficacious for adaptive functioning. Individuals with ASD may be non-verbal, so response to medication is often judged by caregiver report. While this may help assess the effectiveness of the selected medication, it must be remembered that the overall goal of pharmacotherapy is to facilitate the child’s adjustment and engagement with behavioral, educational, and communication interventions.

Intranasal oxytocin (IO) is a novel approach to treating ASD. In preliminary studies, IO leads to increased social interactions, better speech comprehension, reduced repetitive behaviors, and functional MRI evidence of improved social attunement. There is currently a large clinical trial testing the efficacy of IO.

Bibliography is available at Expert Consult.
Bibliography


Psychosis is a severe disruption of thought, perception, and behavior resulting in loss of reality testing. Delusions, hallucinations, disorganized thinking, grossly disorganized behavior, and negative symptoms are key features that define psychotic disorders. Delusions are fixed, unchangeable, false beliefs even in light of conflicting evidence. They may include a variety of themes (persecutory, referential, somatic, religious, or grandiose). Delusions are considered bizarre if they are clearly implausible. Hallucinations are vivid and clear perception-like experiences that occur without external stimulus and have the full force and impact of normal perceptions. They may occur in any sensory modality; auditory hallucinations are the most common. Disorganized thinking is typically inferred from an individual’s speech (loose associations, tangentiality, or incoherence). Grossly disorganized behavior may range from child-like silliness to catatonic behavior. Negative symptoms include diminished emotional expression, avolition, alogia (lack of speech), anhedonia (inability to experience pleasure), and asociality. They generally account for a substantial portion of the morbidity associated with schizophrenia.

### 31.1 Schizophrenia Spectrum and Other Psychotic Disorders

Schizophrenia spectrum and other psychotic disorders include brief psychotic disorder, schizophreniform disorder, schizophrenia, schizoaffective disorder, substance/medication-induced psychotic disorder (see Chapter 114), psychotic disorder caused by another medical condition, catatonia associated with another mental disorder, catatonic syndrome caused by another medical condition, unspecified catatonia, delusional disorder, schizotypal personality disorder, and other specified/unspecified schizophrenia spectrum and other psychotic disorders.

#### DESCRIPTION

The schizophrenia spectrum and other psychotic disorders are primarily characterized by the active (or positive) symptoms of psychosis, specifically delusions, hallucinations, disorganized speech, or grossly disorganized behavior. Brief psychotic disorder is characterized by the sudden onset (within 2 wk from baseline function) of these symptoms in the context of emotional turmoil or overwhelming confusion, followed by complete resolution (Table 31-1). Although brief, the level of impairment in this disorder may be severe enough that supervision may be required to ensure that basic needs are met and the individual is protected from the consequences of poor judgment and cognitive impairment.

If the psychotic symptoms persist for up to 6 mo, the condition is called schizophreniform disorder (Table 31-2), whereas in schizophrenia, there are continuous signs of the disturbance for at least 6 mo (Table 31-3). Active symptoms must have been present for a significant portion of time during a 1 mo period, and the level of psychosocial functioning must be markedly below the level achieved prior to the onset (or there is failure in children to achieve the expected level of functioning).
Schizophrenia is a heterogeneous clinical syndrome with a range of cognitive, behavioral, and emotional dysfunctions. Prodromal symptoms often precede the active phase, in which individuals may express a variety of unusual or odd beliefs and may have unusual perceptual experiences; their speech may be generally understandable but vague; and their behavior may be unusual but not grossly disorganized. Individuals who had been socially active may become withdrawn. Individuals with schizophrenia can display inappropriate affect, dysphoric moods, disturbed sleep patterns, and lack of interest in eating or food refusal. Depersonalization, derealization, somatic concerns, and anxiety and phobias are common. Cognitive deficits are observed, including decrements in declarative memory, working memory, language function, and other executive functions, as well as slower processing speed. These individuals may have no insight or awareness of their disorder, which is a predictor of nonadherence to treatment, higher relapse rates, and poorer illness course. Hostility and aggression can be associated with schizophrenia, although spontaneous or random assault is uncommon. Aggression is more frequent for younger males and for individuals with a past history of violence, non-adherence with treatment, substance abuse, and impulsivity.

The essential features of schizophrenia are the same in childhood, but it is more difficult to make the diagnosis. In children, delusions and hallucinations may be less elaborate, and visual hallucinations may be more common. Disorganized speech and behavior occur in many childhood onset psychiatric disorders, and should not be attributed to schizophrenia unless more common disorders are ruled out.

**CLINICAL COURSE**

Brief psychotic disorder may appear in adolescence or early adulthood, with the average age of onset in the mid-30s. By definition, a diagnosis of brief psychotic disorder requires full remission within 1 mo of onset. The development of schizophreniform disorder is similar to that of schizophrenia. About one-third of individuals with an initial diagnosis of schizophreniform disorder recover within a 6 mo period; the majority of the remaining two-thirds will eventually receive a diagnosis of schizophrenia or schizoaffective disorder.

Schizophrenia typically develops between the late teens and the mid-30s; onset prior to adolescence is rare. The peak age at onset for the first psychotic episode is in the early to mid-20s for males and in the late-20s for females. The onset may be abrupt or insidious, but the majority of individuals manifest a slow and gradual development, with around one-half of individuals complaining of depressive symptoms. The predictors of course and outcome are largely unexplained. The course appears to be favorable in approximately 20% of cases, and a small number of individuals are reported to recover completely. Most individuals require daily living supports. Psychotic symptoms tend to diminish over time, while negative symptoms are the most persistent, along with cognitive deficits.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis for the psychotic disorders is broad, and includes substances/medications (dextromethorphan, LSD, hallucinogenic mushrooms, psilocybin, peyote, cannabinoids, stimulants, and inhalants; corticosteroids, anesthetics, anticholinergics, antihistamines, amphetamines), other medical conditions (Tables 31-4 and 31-5), other disorders within the same class, depressive and bipolar disorders.

**Table 31-3**

<table>
<thead>
<tr>
<th>DSM-5 Diagnostic Criteria for Schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Two (or more) of the following, each present for a significant portion of time during a 1 mo period (or less if successfully treated). At least 1 of these must be (1), (2), or (3): 1. Delusions. 2. Hallucinations. 3. Disorganized speech (e.g., frequent derailment or incoherence). 4. Grossly disorganized or catatonic behavior. 5. Negative symptoms (i.e., diminished emotional expression or avolition).</td>
</tr>
<tr>
<td>B. For a significant portion of the time since the onset of the disturbance, level of functioning in 1 or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).</td>
</tr>
<tr>
<td>C. Continuous signs of the disturbance persist for at least 6 mo. This 6 mo period must include at least 1 mo of symptoms (or less if successfully treated) that meet criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual periods. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).</td>
</tr>
<tr>
<td>D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either (1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.</td>
</tr>
<tr>
<td>E. The disturbance is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.</td>
</tr>
<tr>
<td>F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least a month (or less if successfully treated).</td>
</tr>
</tbody>
</table>


**Table 31-4**

<table>
<thead>
<tr>
<th>Medical Conditions Associated with Psychotic-like Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medications (steroids, β-blocking agents, cyclosporine)</td>
</tr>
<tr>
<td>Drugs of abuse (intoxication, overdose or withdrawal)</td>
</tr>
<tr>
<td>Central nervous system infections</td>
</tr>
<tr>
<td>Autoimmune encephalitis (anti-N-methyl-D-aspartate [NMDA] receptor/limbic/paraneoplastic)</td>
</tr>
<tr>
<td>Acute disseminated encephalomyelitis (ADEM)</td>
</tr>
<tr>
<td>Systemic lupus erythematosus (SLE)</td>
</tr>
<tr>
<td>Syndromes (fragile X, trisomy 21, tuberous sclerosis)</td>
</tr>
<tr>
<td>Wilson disease</td>
</tr>
<tr>
<td>Porphyria</td>
</tr>
<tr>
<td>Nonconvulsive status (seizures)</td>
</tr>
<tr>
<td>Hyper/hypoparathyroidism</td>
</tr>
<tr>
<td>Hyper/hypothyroidism</td>
</tr>
<tr>
<td>Hyper/hypoadrenalinism</td>
</tr>
<tr>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Thiamine deficiency</td>
</tr>
<tr>
<td>Vitamin B₁₂ deficiency</td>
</tr>
<tr>
<td>Inborn errors of metabolism (see Table 31-5)</td>
</tr>
</tbody>
</table>

**Epidemiology**

Brief psychotic disorders have been reported to account for 9% of cases of first-onset psychosis in the United States with a 2:1 ratio in favor of females. The incidence of schizophreniform disorders in the United States and other developed countries appears as much as 5-fold less than that of schizophrenia, whereas in developing countries the incidence is higher (approaching that of schizophrenia), particularly when associated with good prognostic features.

The lifetime prevalence of schizophrenia is approximately 0.3–0.7%, although there are reported variations by race/ethnicity, across countries, and by geographic origin for immigrants. The male: female ratio is approximately 1.4:1. Males generally have a worse premorbid adjustment, lower educational achievement, more prominent negative symptoms, and more cognitive impairment than females.
Table 31-5 Psychiatric Signs in Inborn Errors of Metabolism in Adolescents and Adults: Review of the Literature and Personal Experience

<table>
<thead>
<tr>
<th>Condition</th>
<th>Confusion</th>
<th>Mental Retardation</th>
<th>Behavioral Disturbances</th>
<th>Catatonia</th>
<th>Visual Hallucinations</th>
<th>Psychosis (Schizophrenia)</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea cycle defects</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cbl (C, G)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>MTHFR deficiency</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Porphyria</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Wilson disease</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>CBS deficiency</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CTX</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>MLD</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>GM2 gangliosidosis</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>NPC</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>α-Mannosidosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>β-Mannosidosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>ALDc</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nonketotic hyperglycinemia</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monoamine oxidase A deficiency</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatine transporter deficiency</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Succinic semialdehyde dehydrogenase deficiency</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

+ Frequently reported; +/-, unusual; empty cell, not reported; ALDc, cerebral adrenoleukodystrophy; CBS, cystathionine β-synthase; CTX, cerebrotendinous xanthomatosis; MLD, metachromatic leukodystrophy; MTHFR, methylene tetrahydrofolate reductase; NPC, Niemann-Pick type C.

(see Chapter 26), malingering and factitious disorders, obsessive-compulsive (see Chapter 25) and body dysmorphic disorder, posttraumatic stress disorder (see Chapter 25), autism spectrum disorder (see Chapter 30) or other communication disorders (see Chapter 35), and personality disorders.

Autoimmune encephalitis caused by anti-N-methyl-D-aspartate (NMDA) receptor or other autoantibodies may manifest with psychosis, anxiety, depression, agitation, aggression, delusions, catatonia, hallucinations, and paranoia in combination with sleep disturbances, autonomic dysfunction (hypoventilation), dyskinesias, movement disorders, seizures, and a depressed level of consciousness. The electroencephalogram (EEG), cerebral spinal fluid, and MRI are usually, but not always, abnormal. The constellation of psychosis and encephalitic features should suggest the diagnosis; however, at presentation behavioral problems may be the dominant feature (see Chapter 598.4).

Differentiating medical from psychiatric causes of abnormal behavior may be difficult. In general, medical causes are often associated with abnormalities in vital signs and the neurologic exam (including level of consciousness). In medical causes of abnormal behavior, there may not be a positive family history or a prior personal history of psychiatric illness. Furthermore, in medical causes, there are often impairments in attention, orientation, recent memory, and intellectual function. Hallucinations may be present with medical disease, but they are often tactile, visual, or olfactory rather than auditory (noted in psychiatric disease). Medical patients may be able to reality test about their hallucinations, stating they are aware they are not real.

The diagnosis of a psychotic disorder should be made only after these other explanations for the observed symptoms have been ruled out. Most children who report hallucinations do not meet criteria for the schizophrenia spectrum disorders, and most do not have psychosis. Normative childhood experiences, including overactive imaginations and vivid fantasies, can be mistaken for psychosis.

COMORBIDITY

Rates of comorbidity with substance-related disorders are high in schizophrenia. Other common comorbidities are anxiety disorders and obsessive-compulsive disorders.

SEQUELAE

Follow-up studies of early onset schizophrenia suggest moderate to severe impairment across the life span. Poor outcome is predicted by low premorbid functioning, insidious onset, higher rates of negative symptoms, childhood onset, and low intellectual functioning. When followed into adulthood, youth with schizophrenia demonstrated greater social deficits, lower levels of employment, and were less likely to live independently, relative to those with other childhood psychotic disorders.

Approximately 5-6% of individuals with schizophrenia die by suicide, approximately 20% attempt suicide on 1 or more occasions, and many more have suicidal ideation. Life expectancy is reduced in individuals with schizophrenia because of associated medical conditions; a shared vulnerability for psychosis and medical disorders may explain some of the medical comorbidity of schizophrenia.

ETIOLOGY AND RISK FACTORS

Etiologic evidence for schizophrenia supports a neurodevelopmental and neurodegenerative model with multiple genetic and environmental exposures playing important roles. It has been hypothesized that while psychotic disorders likely have their origins in early development, but it is not until they are in their mid-teens that the underlying neural structures manifest the disabling functional deficits and resultant psychotic symptoms.

Genetic Factors

The lifetime risk of developing schizophrenia is 5-20 times higher in 1st-degree relatives of affected probands compared to the general population. Concordance rates of 40-60% and 5-15% have been reported, respectively, in monozygotic and dizygotic twins. Genome-wide association studies, using large collaborative international cohorts, have implicated different genomic loci and genes, including the major histocompatibility complex (6p21.1), MIR137, and ZNF804a. Structural mutations arising at genomic "hotspots," including 1q21.1, 15q13.3, and 22q11.2, may be responsible for 0.5-1.0% of cases.

Childhood schizophrenia appears to be associated with a higher rate of large cytogenetic abnormalities and rare structural variants than reported in adults. The majority of rare copy number errors detected in affected persons are found at different genetic loci, and many are unique to 1 individual or family.

Environmental Factors

In utero exposure to maternal famine, advanced paternal age, prenatal infections, obstetric complications, marijuana use and immigration have been hypothesized to contribute to the development of schizophrenia. Environmental exposures may mediate disease risk via direct neurologic damage, gene by environment interactions, epigenetic effects and/or de novo mutations. There is no evidence that psychological or social factors cause schizophrenia. Rather, environmental factors may potentially interact with biologic risk factors to mediate the timing of onset, course, and severity of the disorder. Expressed emotion within the family setting can influence the onset and/or exacerbation of acute episodes and relapse rates.

Neuroanatomical Abnormalities

Increased lateral ventricle volumes along with reductions in hippocampus, thalamus, and frontal lobe volumes have been reported in schizophrenia. Youth in particular have reductions in grey matter volumes and reduced cortical folding. Neurotransmitter systems, particularly central nervous system dopamine circuits, are hypothesized to have a key role in the pathophysiology of schizophrenia. The dopamine hypothesis is derived in part from the identification of D2 receptor blockade as the mechanism for the action of antipsychotic medications.

PREVENTION

There has been significant interest in prospectively identifying youth at risk for schizophrenia spectrum and other psychotic disorders in an effort to provide early intervention prior to the development of a full-blown psychotic disorder. Various names including attenuated psychosis syndrome (APS), psychosis risk syndrome, ultrahigh risk, clinical high risk, at-risk mental state, and prodromal stage have been used to describe patients that present with troubling symptoms suggestive of early psychosis.

APS is characterized by the presence of delusions, hallucinations, or disorganized speech in an attenuated form, with relatively intact reality testing, but of sufficient frequency to warrant clinical attention. Symptoms are described as being present at least once per week for the past month and have begun/worsened over the past year. The symptoms are less severe and more transient than a psychotic disorder, although nearly 20-40% with these attenuated symptoms appear to go on to a psychotic disorder within 3 yr of symptom presentation. There is evidence that premorbid lower cognitive and social skills as well as a history of substance abuse contribute to the risk of developing a full-blown psychotic disorder in individuals with APS.

There is some evidence that antipsychotic medication may delay conversion of attenuated to full-blown psychosis and ameliorate attenuated symptoms in active treatment, yet there appear to be no lasting effects after the medication is withdrawn. In addition, there is concern that the long-term use of even low-dose antipsychotic medication may cause heightened sensitization of brain dopamine receptors, which, in turn, could lead to a rapid-onset of psychosis following discontinuation of the medication.

Antidepressants have been associated with symptomatic improvement in adolescents with APS. In a randomized control trial, omega-3 fish oils reduced attenuated positive, negative, and general symptoms. Psychological interventions (social skills, cognitive, and interaction training programs, as well as psychoeducational family interventions and cognitive-behavioral therapy) are reported to improve symptoms and psychosocial functioning in youth with early symptoms.
Despite improvements in diagnostic predictive validity, significant concern remains regarding a high false-positive rate (identifying an individual as prodromal who does not go on to develop psychosis) that may cause individuals to be stigmatized or exposed to unnecessary treatment. In this context, youth with early symptoms suggestive of psychosis should be referred to a child and adolescent psychiatrist and/or a specialized research program.

**SCREENING/CASE FINDING**

Pediatric practitioners can make general inquiries of youth and their parents regarding problems with thinking or perceptions. For the older youth, questions like “Does your mind ever play tricks on you?” “Do you hear voices talking to you when no one is there?” and/or “Does your mind ever feel confused?” can help elicit symptoms. For younger children, the clinician must ensure that the child understands the questions. True psychotic symptoms are generally confusing to the individual, and highly descriptive, detailed, organized, and/or situation-specific reports are less likely to represent true psychosis. Overt signs of the illness should be evident on mental status exam; without overt evidence of psychosis, the validity of symptom reports needs to be carefully scrutinized. For youth presenting with what could be psychosis, assessment and treatment in the specialty mental health setting by a child and adolescent psychiatrist should be provided.

**ASSESSMENT**

The diagnostic assessment of schizophrenia in youth is uniquely complicated and misdiagnosis is common. Most children who report hallucinations do not meet criteria for schizophrenia, and many do not have a psychotic illness. Normative childhood experiences, including overactive imaginations and vivid fantasies, can be misinterpreted as psychosis. Expertise in childhood psychopathology and experience in assessing reports of psychotic symptoms in youth are important prerequisites for clinicians evaluating youth for possible psychosis. Comprehensive diagnostic assessments, which reconcile mental status findings with the rigorous application of diagnostic criteria, help improve accuracy.

There are no neuroimaging, psychological or laboratory tests that establish a diagnosis of schizophrenic spectrum disorders. The medical evaluation focuses on ruling out nonpsychiatric causes of psychosis, while also establishing baseline laboratory parameters for monitoring medication therapy. Routine laboratory testing typically includes blood counts, basic metabolic panel, liver and renal functions, metabolic parameters, and thyroid functions. More extensive evaluation is indicated for atypical presentations, such as a gross deterioration in cognitive and motor abilities, focal neurololgic symptoms, or delirium. Neuroimaging may be indicated when neurologic symptoms are present, or an EEG is indicated for a clinical history suggestive of seizures. Toxicology screens are indicated for acute onset or exacerbations of psychosis, when exposure to drugs of abuse cannot be ruled out. Genetic testing is indicated if there are associated dysmorphic or syndromic features. Tests to rule out specific syndromes or diseases (e.g., amino acid screens for inborn errors of metabolism, ceruloplasmin for Wilson disease [see Chapter 357.2], porphobilinogen for acute intermittent porphyria [see Chapter 91]) are indicated for clinical presentations suggestive of a specific syndrome. Neuropsychological testing cannot establish the diagnosis, but may be important for documenting cognitive deficits for academic planning.

**TREATMENT**

There are hallmark phases important to recognize in the assessment and management of schizophrenia. In the prodrome phase, most patients experience functional deteriorations (i.e., social withdrawal, idiosyncratic preoccupations, unusual behaviors, academic failure, deteriorating self-care skills, and/or dysphoria) prior to the onset of psychotic symptoms. The acute phase is characterized by prominent positive symptoms and deterioration in functioning. The recuperative/recovery phase is marked by a several-month period of impairment and predominantly negative symptoms. The residual phase (if reached) has no positive symptoms though negative symptoms may contribute to some level of impairment.

Treatment goals include decreasing psychotic symptomology, directing the child toward a developmentally typical trajectory, and reintegrating the child into the home and community. Children and families facing schizophrenia spectrum disorders require an array of mental health services to address their psychological, social, educational, and cultural needs. Given the insidious onset and chronic course of these disorders, the patient must be followed longitudinally, with periodic reassessment to hone diagnostic accuracy and tailor services to meet the patient’s and family’s needs. Integrated psychopharmacologic, psychotherapeutic, psychoeducational, and case-management services are often necessary.

Psychoeducation about the illness with an assessment of the potential role of stigma in treatment participation is critical for improving adherence with treatment recommendations. Assessing a child’s strengths and vulnerabilities as well as available environmental resources is critical in devising an effective treatment plan. School and community liaison work to develop and maintain a day-to-day schedule for the patient is important. Specialized educational programs should be considered within the school system. Cognitive remediation has shown some promising results in planning ability and cognitive flexibility. Effective and collaborative communication among the family, the pediatrician, a child and adolescent psychiatrist, and other mental health providers increases the potential for the patient’s optimal functioning.

**Pharmacotherapy**

First-generation (typical) and second-generation (atypical) antipsychotic medications have been shown to be effective in reducing psychotic symptoms with the latter the preferred medication choice (see Chapter 21). Haloperidol, risperidone, aripiprazole, quetiapine, paliperidone, and olanzapine are FDA approved for treating schizophrenia in ages 13 yr and older. The choice of which agent to use first is typically based on FDA approval status, side-effect profile, patient and family preference, clinician familiarity, and cost. Depot antipsychotics have not been studied in pediatric age groups and have inherent risks with long-term exposure to side effects. Although clozapine is effective in treating both positive and negative symptoms, its risk for agranulocytosis and seizures limits its use to those patients with treatment-resistant disorders.

Most patients require long-term treatment and are at significant risk to relapse if their medication is discontinued. The goal is to maintain the medication at the lowest effective dose so as to minimize potential adverse events. Many patients will continue to experience some degree of positive or negative symptoms, requiring ongoing treatment. Patients should maintain regular physician contact so as to monitor symptom course, side effects, and adherence.

Individuals prescribed antipsychotic medications need to be systematically monitored for side effects, including sedation, abnormal movements, weight gain, hyperprolactinemia, elevated liver transaminases, diabetes, hyperlipidemia, hematologic effects (leukopenia or neutropenia), seizures, neuroleptic malignant syndrome, and cardiovascular effects. For atypical antipsychotics, body mass index, fasting blood glucose, fasting triglycerides/cholesterol, waist circumference, high-density lipoprotein/low-density lipoprotein, blood pressure, and symptoms of diabetes should be checked at baseline and at regular intervals thereafter. Regular physical activity and nutritional balance should be part of a comprehensive treatment plan.

Abnormal movements (dystonia, akathisia, tardive dyskinesia) need periodic assessment preferably using a standardized instrument such as the Abnormal Voluntary Movement Scale (AIMS). The need for antiparkinsonian agents may be a consideration for patients, particularly those at risk for acute dystonia or who have a previous history of dystonic reactions. In patients with a personal or family history of cardiac abnormalities, including syncpe, palpitations, arrhythmias, or sudden unexplained death, a baseline electrocardiogram with subsequent monitoring should be considered, along with cardiology consultation. Alternative pharmacology should be considered if the resting
heart rate exceeds 130 beats/min, or the PR, QRS, and QTc exceed 200, 120, and 460 msec, respectively.

Electroconvulsive therapy (ECT) may be used with severely impaired adolescents if medications are either not helpful or cannot be tolerated. It has not been systematically studied in children.

**Bibliography is available at Expert Consult.**

### 31.2 Psychosis Associated with Epilepsy

**David R. DeMaso**

Schizophrenia spectrum and other psychotic disorders include psychotic disorder due to another medical condition (Table 31-6). Psychosis associated with epilepsy has been reported in children and adults. Also called schizophrenic-like psychosis of epilepsy, the disorder manifests with delusions or hallucinations, along with poor insight. The characterization is complicated by the fact that anticonvulsant drugs can present with psychosis and antipsychotic drugs can lower the seizure threshold, producing seizures.

Psychosis associated with epilepsy can be further differentiated into ictal, interictal, and postictal psychosis. Ictal-induced psychosis is a form of nonconvulsive status epilepticus, usually complex partial status that can last for hours to days and is associated with periods of impaired consciousness. Brief interictal psychosis can last days to weeks and is associated with paranoia, delusions, and auditory hallucinations. Chronic interictal psychosis resembles schizophrenia and manifests with paranoia, visual hallucinations, and catatonia. Postictal psychosis is the most common type (observed in 2-7% of patients with epilepsy); it lasts up to 1 wk and then spontaneously remits.

The diagnosis requires a strong index of suspicion and EEG monitoring. Treatment requires appropriate anticonvulsant drugs and, if the psychosis persists, initiating low-dose antipsychotic medication.

**Bibliography is available at Expert Consult.**

### 31.3 Catatonia in Children and Adolescents

**Bonita F. Stanton**

Catatonia is a poorly defined state presenting as an unusual manifestation of decreased or increased muscle tone and decreased responsiveness (although agitation may be present) occurring in association with a broad array of conditions affecting children, adolescents and adults. These conditions include psychosis, autism spectrum disorder, developmental disorders, drug-induced conditions, affective disorders and a wide range of medical disorders (Table 31-7). Not surprising given the ill-defined nature of the condition, the prevalence of catatonia in children and adolescents is unknown, although it is generally believed to be significantly underdiagnosed. Recognition of catatonia by a clinician is very important because the disorder is generally very responsive to treatment with benzodiazepines and/or ECT.

**DIAGNOSIS AND TREATMENT**

Catatonia is defined as 3 or more of the 12 symptoms listed in Table 31-8. An important next step is the evaluation and possible elimination of medications being administered to the child for their potential to induce catatonic symptoms, a not-infrequent side effect of many medical and psychiatric medications. Of particular importance, antipsychotic agents should be discontinued as they have been associated with an increased incidence of malignant catatonia or neuroleptic malignant syndrome (see Chapter 21).

Benzodiazepams (typically lorazepam) and ECT are effective in adults and appear to be effective in children. A treatment algorithm using a lorazepam challenge test (by mouth, intravenous, or intramuscular administration of lorazepam 1-2 mg) is shown in Figure 31-1. If the challenge test does reverse symptoms, increasing doses of lorazepam are indicated, with careful monitoring to avoid side effects. ECT may be indicated alone (if no improvement with lorazepam) or in combination with lorazepam if some but incomplete improvement is noted.

**Table 31-7 Conditions Associated with Catatonia**

<table>
<thead>
<tr>
<th>Psychotic disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paranoid schizophrenia, catatonic schizophrenia, psychosis, schizophrenia, Prader-Willi syndrome, intellectual impairment</td>
</tr>
<tr>
<td>Mood disorders</td>
</tr>
<tr>
<td>Bipolar disorder—manic or mixed episodes</td>
</tr>
<tr>
<td>Major depressive disorder</td>
</tr>
<tr>
<td>Medical conditions</td>
</tr>
<tr>
<td>Endocrine abnormalities, infections, electrolyte imbalances</td>
</tr>
<tr>
<td>Neurologic conditions</td>
</tr>
<tr>
<td>Epilepsy, strokes, traumatic brain injury, multiple sclerosis, encephalitis</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>Withdrawal: Benzodiazepines, L-dopa, gabapentin</td>
</tr>
<tr>
<td>Overdose: LSD, phencyclidine (PCP), cocaine, Ecstasy, disulfiram, levetiracetam</td>
</tr>
</tbody>
</table>


**Table 31-8 Diagnostic Criteria of Catatonia in the DSM-5**

<table>
<thead>
<tr>
<th>Catatonia is defined as the presence of 3 or more of the following</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cataplexy (i.e., passive induction of a posture held against gravity)</td>
</tr>
<tr>
<td>2. Waxy flexibility (i.e., slight and even resistance to positioning by examiner)</td>
</tr>
<tr>
<td>3. Stupor (no psychomotor activity; not actively relating to environment)</td>
</tr>
<tr>
<td>4. Agitation, not influenced by external stimuli</td>
</tr>
<tr>
<td>5. Mutism (i.e., no, or very little, verbal response [Note: not applicable if there is an established aphasia])</td>
</tr>
<tr>
<td>6. Negativism (i.e., opposing or not responding to instructions or external stimuli)</td>
</tr>
<tr>
<td>7. Posturing (i.e., spontaneous and active maintenance of a posture against gravity)</td>
</tr>
<tr>
<td>8. Mannerisms (i.e., odd caricature of normal actions)</td>
</tr>
<tr>
<td>9. Stereotypes (i.e., repetitive, abnormally frequent, non–goal-directed movements)</td>
</tr>
<tr>
<td>10. Grimming</td>
</tr>
<tr>
<td>11. Echolalia (i.e., mimicking another’s speech)</td>
</tr>
<tr>
<td>12. Echopraxia (i.e., mimicking another’s movements)</td>
</tr>
</tbody>
</table>


Among adults, hallucinations are viewed as synonymous with psychosis and as harbingers of serious psychopathology. In children, hallucinations can be part of normal development or can be associated with nonpsychotic psychopathology, psychosocial stressors, drug intoxication, or physical illness. The first clinical task in evaluating youth who report hallucinations is to sort out those that are associated with severe mental illness from those that derive from other causes (Fig. 31-2).

**CLINICAL MANIFESTATIONS**

Hallucinations are perceptions (typically auditory, visual, tactile, or olfactory) that occur in the absence of identifiable external stimuli. Hallucinations can be further categorized as nondiagnostic (hearing footsteps, knocking, or one's name) and diagnostic (hearing 1 or more voices saying words other than one's own name).

In children with nonpsychotic hallucinations, the symptoms of psychosis are absent. Nonpsychotic hallucinations commonly occur in the context of severe traumatic stress, developmental difficulties, social and emotional deprivation, parents whose own psychopathology promotes a breakdown in the child's sense of reality, cultural beliefs in mysticism, and unresolved mourning. Auditory hallucinations of voices telling the child to do bad things may be more often associated with disruptive behavior disorders than with psychotic diagnoses. Hearing a voice invoking suicide is often associated with depression. Trauma-related auditory hallucinations are commonly associated with posttraumatic stress disorder or a brief psychotic disorder with marked stressors. The content of the hallucinations may be relevant in understanding the underlying psychopathology and/or developmental issues.
Bibliography
DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Acute phobic hallucinations are benign and common and occur in previously healthy preschool children. The hallucinations are often visual or tactile, last 10-60 minutes, and occur at any time but most often at night. The child is quite frightened and might complain that bugs or snakes are crawling over him or her and attempt to remove them. The cause is unknown. The differential diagnosis includes drug overdose or poisoning, high fever, encephalitis, and psychosis. The child's fear is not alleviated by reassurance by the parents or physician, and the child is not amenable to reason. Findings on physical and mental status examinations are otherwise normal. Symptoms can persist for 1-3 days, slowly abating over 1-2 wk.

The differential diagnosis of hallucinations comprises a broad range of mental disorders, including diagnoses in which hallucinations are not the hallmark feature, but may be viewed as associated symptoms (posttraumatic stress disorder, nonpsychotic mood disorders, and disruptive, impulse-control, and conduct disorders); diagnoses that are defined by psychotic features (brief psychotic disorder, schizophrenia, major depressive or bipolar disorder with psychotic features); and at-risk clinical states (poor reality testing). In addition, other medical conditions can manifest with hallucinations, including drug intoxications (cannabis, LSD, cocaine, amphetamines, barbiturates), medication side effects (e.g., steroids, anticholinergic medications, stimulant medications), and physical illnesses (e.g., thyroid, parathyroid, and adrenal disorders; Wilson disease; electrolyte imbalances; infections; migraines; seizures; and neoplasms).

TREATMENT

The evaluation of the underlying condition directs the type of treatment needed. Nonpsychotic hallucinations suggest the need for disorder-specific psychotherapy (e.g., trauma-focused cognitive behavioral therapy for posttraumatic stress disorder) and perhaps adjunctive medication (e.g., an antidepressant for depression or anxiety, or a brief trial of antipsychotic medication for agitation). Cognitive-behavioral therapy focused on helping the youth understand the origin of the hallucinations and on developing coping strategies for stressful situations may be helpful for older children and adolescents. True psychotic hallucinations suggest the need for antipsychotic medication.

Bibliography is available at Expert Consult.
Bibliography
Learning Disorders

Chapter 32
Neurodevelopmental Function and Dysfunction in the School-Age Child
Desmond P. Kelly and Mindo J. Natale

TERMINOLOGY AND EPIDEMIOLOGY
A neurodevelopmental function is a basic brain process needed for learning and productivity. Neurodevelopmental variation refers to differences in neurodevelopmental functioning. Wide variations in these functions exist within and between individuals. These differences can change over time and need not represent pathology or abnormality.

Neurodevelopmental dysfunctions reflect disruptions of neuroanatomic structure or psychophysio logic function and place a child at-risk for developmental, cognitive, emotional, behavioral, psychosocial and adaptive challenges. For the school-age child, an area of particular focus is academic skill development. Academic disorders have been diagnostically classified as Specific Learning Disorder (SLD) by the revised Diagnostic and Statistical Manual of Mental Disorder Fifth Edition (DSM-5). Changes in DSM-5 (compared to DSM-IV) involve a broadening of the diagnostic criteria in an effort to recognize factors that may interrupt the effective acquisition of academic skills that include reading, written language, spelling and mathematics. The International Classification of Diseases (ICD) of the World Health Organization, 10th Edition (ICD-10) categorizes Specific Developmental Disorders of Scholastic Skills that include Reading Disorder, Spelling Disorder, Disorder of Arithmetical Skills, and Mixed Disorder of Scholastic Skills. Dyslexia (reading disorder) is included in ICD-10 in a separate category of symbolic dysfunction. The terms, Dyscalculia (mathematics disorder), and Dysgraphia (written language disorder) are also used by investigators and clinicians, but their inclusion in diagnostic classification systems has been inconsistent and a source of some disagreement among experts.

Traditionally, the educational system has identified SLDs through the process of psychoeducational testing. Through this process, students experiencing academic problems would be evaluated psychometrically. Typical testing batteries have usually included measures of overall intelligence and academic skills. A student exhibiting a significant discrepancy between scores on tests of intelligence and tests of academic achievement could be classified as a student with an SLD, and would subsequently be eligible for Special Education Services. The degree of discrepancy required for such classification often differed between states and even between school districts. In a marked change in approach to the identification of SLDs, the reauthorization of the Individuals with Disabilities Education Act (IDEA) in 2004 introduced the Response to Intervention (RTI) model, which does not necessitate that schools use the discrepancy model for determining if a student has an SLD. Instead, schools may employ research-based intervention approaches and monitor a student’s response to that intervention before initiating psychoeducational testing. This approach has been met with some disapproval, as those who challenge its effectiveness argue that the RTI model, in and of itself, should not be used to identify children with SLD. The underlying view behind this objection rests with the notion that children may fail to respond to RTI for a variety of reasons (e.g., underlying neurocognitive weakness), not just because a SLD exists.

Overall estimates of the prevalence of SLD’s range from 3-10%. Some data indicate that approximately 8% of children 3-17 yr of age have, at one point, been identified as having a SLD. Prevalence estimates can vary owing to numerous factors, including differences in definitions and criteria used for classification and diagnosis, as well as differences in methods of assessment.

ETIOLOGY AND PATHOGENESIS
Neurodevelopmental dysfunction may present for any number of reasons. These include pre-/perinatal, genetic, medical, psychologic, environmental and sociocultural influences. Genes that contribute to neurodevelopmental dysfunction have been identified. Reading disorders can be both familial and heritable, and studies have linked some reading disabilities to specific gene loci on chromosomes 6 and 15. Chromosomal abnormalities can lead to unique patterns of dysfunction, such as visual–spatial deficits in girls diagnosed with Turner syndrome or language deficits in children with fragile X syndrome (see Chapter 81). Chromosome 22q11.2 deletion syndrome (DiGeorge or velocardiofacial syndrome [see Chapter 125]) is associated with predictable patterns of neurodevelopmental dysfunction, including a higher prevalence of intellectual disability, and deficits in visual–spatial processing, executive function, attention, working memory, verbal learning, arithmetic, and language with relative strengths in selected reading and spelling skills. Investigations of the neuroanatomical substrates have also yielded important information about the underlying causes of neurodevelopmental dysfunction. Multiple investigations have identified differences in the left parietotemporal and left occipitotemporal brain regions of individuals with dyslexia compared to those without reading difficulties (see Chapter 34). Studies also describe the neural circuitry, primarily in the parietal cortex, underlying mathematical competencies such as the processing of numerical magnitude, and mental arithmetic investigations support a broader role for the white matter in active learning and memory than was previously estimated.

Perinatal risk factors that are associated with neurodevelopmental dysfunction include very-low birthweight, severe intrauterine growth restriction, perinatal hypoxic–ischemia encephalopathy, and prenatal exposure to substances such as alcohol and drugs (see Chapter 96). Increased risk of academic and frontal lobe disorders also is associated with environmental toxins, including lead (see Chapter 721); drugs such as cocaine; infections such as meningitis and HIV; and brain injury secondary to intraventricular hemorrhage, periventricular leukomalacia, or head trauma.

Early psychologic trauma can result in both structural and neurochemical changes in the developing brain, which may contribute to neurodevelopmental dysfunction. Findings suggest that the effects of exposure to trauma (see Chapter 39) and/or abuse (see Chapter 40) early in the developmental course can induce disruption of the brain’s regulatory system with connections in the orbitofrontal cortex, and may influence right-hemisphere function with associated risk for problems with information processing, memory, and frontal lobe related operations (e.g., focus and self-regulation). Environmental and sociocultural deprivation can lead to, or potentiate, neurodevelopmental dysfunction, which most often results from a combination of contributing factors, rather than a single cause.
CORE NEURODEVELOPMENTAL FUNCTIONS

The neurodevelopmental processes that are critical for academic success may best be understood as falling within core neurodevelopmental domains.

Sensory and Motor Development

Sensory development (e.g., auditory, visual, tactile, proprioceptive) begins well before birth. This neurodevelopmental process is crucial in helping children experience, understand, and manipulate their environments. Through sensory experiences, children’s brains mature as new neuronal pathways are created and existing pathways are strengthened. Any interruption of this process may result in sensory-motor deficits and delays (e.g., apraxia) that can interfere with early development and academic performance.

Sensory development for the school-age child progresses in association with environmental exposure and with the development of other cognitive processes such as motor development.

There are 3 distinct, yet related, forms of neuromotor ability: graphomotor, fine motor, and gross motor coordination.

Graphomotor function refers to the specific motor aspects of written output. Several subtypes of graphomotor dysfunction significantly impede writing. Some children harbor weaknesses of visualization during writing. They have trouble picturing the configurations of letters and words as they write (orthographics). Their written output tends to be poorly legible, with inconsistent spacing between words. Others have weaknesses in orthographic memory, which interferes with their ability to recall and/or reproduce letter and number forms rapidly and accurately. They may labor over individual letters and prefer printing (manuscript) to cursive writing. Some exhibit signs of finger agnosia or weak graphomotor feedback; they have trouble localizing their fingers while they write. As a result, they need to keep their eyes very close to the page and tend to apply excessive pressure to the pencil. Others struggle with graphomotor production deficits. For these children, trouble producing the highly coordinated motor sequences needed for writing results in difficulty assigning writing roles to specific muscle groups in their hands. This phenomenon has also been described as dyspraxic dysgraphia. It is important to emphasize that a child may show excellent fine motor dexterity (as revealed in mechanical or artistic domains) but very poor graphomotor fluency (with labored or poorly legible writing).

For the school-age child, problems with fine motor function can disrupt their ability to communicate in written form, to excel in artistic and crafts activities, and can interfere with learning a musical instrument or mastering a computer keyboard. The term dyspraxia relates to difficulty in developing an ideomotor plan and activating coordinated and integrated visual motor actions to complete a task or solve a motor problem, such as assembling a model.

Some children exhibit gross motor incoordination. They have problems in processing “outer spatial” information to guide gross motor actions. Affected children may be inept at catching or throwing a ball because they cannot form accurate judgments about trajectories in space. Others demonstrate diminished body position sense. It may be hard for them to recall or plan complex motor procedures such as those needed for dancing, gymnastics, or swimming. Children with gross motor problems can incur considerable embarrassment in physical education classes. Gross motor weaknesses can lead to social rejection, withdrawal, and generalized feelings of inadequacy.

Language

Language is one of the most critical and complex cognitive functions and can be broadly divided into receptive (auditory comprehension/understanding) and expressive (speech and language production and/or communication) functions. Children who primarily experience receptive language problems may have difficulty understanding verbal information, following instructions and explanations, and interpreting what they hear. Expressive language weaknesses can result from problems with speech production and/or problems with higher level language development (see Chapter 35). Speech production difficulties include oromotor problems affecting articulation, verbal fluency, and naming. Some children have trouble with sound sequencing within words. Others find it hard to regulate the rhythm or prosody of their verbal output. Their speech may be dysfluent, hesitant, and inappropriate in tone. Problems with word retrieval can result in problems in finding exact words when needed (as in a class discussion) or substituting definitions for words (circumlocution). Children who evidence higher level expressive language impediments have trouble formulating sentences, using grammar acceptably, and organizing spoken (and possibly written) narratives.

In considering disordered language, whether in reception or expression, it is vital to ascertain the potential underlying difficulties that are contributing. Some children, for example, have particular problems with phonology (see Chapter 35). Commonly, a weak phonologic sense has a negative effect not only on language processing, but also on the development of reading, writing and even mathematics (e.g., word problems). Children with semantic deficits have trouble learning the meaning of words, and as a result, may use words improperly (e.g., out of context). Other common language deficiencies include difficulty with syntax (word order), problems with discourse (paragraphs and passages), an underdeveloped sense of metalinguistics (the ability to think about and analyze how language works), and trouble with drawing appropriate inferences (supplying missing information) from language. Difficulty with language pragmatics, or the social understanding and application of language, can be another significant impediment.

Language weaknesses not only contribute to problems with reading, writing and math, but can also manifest in the content areas, such as the sciences, which necessitate the processing of dense verbal material in textbooks and the rapid convergent recall of facts, and social studies courses that often entail the use of sophisticated language and verbal abstract concepts (e.g., democracy). Learning foreign languages can be a serious problem. In contrast, children who possess strong language skills are often able to make use of their linguistic facility to compensate for any academic problems; it may be possible to verbalize one’s way through a mathematics curriculum, thereby circumventing a tendency to be confused by predominantly nonverbal concepts (e.g., ratio, equation, and diameter).

To one degree or another, all academic skills are taught largely through language, and thus it is not surprising that children who experience language dysfunction often experience problems with academic performance. In fact, some studies suggest that up to 80% of children who present with a SLD also experience language-based weaknesses.

Visual-Spatial/Visual-Perceptual Function

The process of visual development begins well before birth, with continued development and refinement throughout childhood (see Chapter 621). Important structures involved in the development and function of the visual system, beyond the eyes themselves, include the retina, optic cells (e.g., rods and cones), the optic chiasm, the optic nerves, the brainstem (control of automatic responses like pupil dilation), the thalamus (e.g., lateral geniculate nucleus for form, motion, color), and the primary (visual space and orientation) and secondary (color perception) visual processing regions located in and around the occipital lobe. Other brain areas, considered to be outside of the primary visual system, are also important to visual function, helping to process what (temporal lobe) is seen and where it is located in space (parietal lobe). The left and right cerebral hemispheres interact considerably in visual processes, with each hemisphere possessing more specialized functions, including left hemisphere mediated processing of details, patterns, and linear information, and right hemisphere processing of the gestalt and overall form.

Some of the more critical aspects of visual processing to develop in the school-age child include spatial relations—the ability to accurately perceive objects in space in relation to other objects; visual
discrimination—the ability to differentiate and identify objects based on their individual attributes such as size, shape, color, form, and position; and, visual closure—the ability to recognize or identify an object even when the entire object cannot be seen.

Children with subtle visual deficits are often misidentified and/or missed completely. Indications of visual processing deficits in the school-age child may include difficulty learning to draw and write, and problems with art activities. These children might also have trouble discriminating between left and right. They might encounter problems recognizing letters and words, resulting in delayed reading, spelling, and writing.

Visual–spatial processing dysfunctions are not a common cause of chronic reading disorders, but more recent investigations have established that deficits in orthographic coding (visual–spatial analysis of character-based systems) can contribute to reading disorders. Spelling and writing can emerge as a weakness because children with visual processing problems commonly have trouble with the precise visual configurations of words. In mathematics, these children often have difficulty with visual–spatial orientation, with resultant difficulty aligning digits in columns when performing calculations and/or difficulty managing geometric material. In the social realm, intact visual processing allows a child to make use of visual or physical cues when communicating and interpreting the paralinguistic aspects of language. Secure visual functions are also necessary to process proprioceptive and kinesthetic feedback to coordinate movements during physical activities. Children with visual processing deficits are thus susceptible to problems such as social isolation and withdrawal and consequent behavioral and/or emotional difficulties.

**Intellectual Function**

The concept of intellectual function, or intelligence, has had many definitions and theoretical models, and achieving a consensus on the subject has been challenging. Well-known theories include Spearman's unitary concept of "the g-factor," the "verbal and nonverbal" theories (e.g., Binet, Thorndike), the 2-factor theory from Catell (crystallized vs fluid intelligence), Luria's simultaneous and successive processing model, and more recent models that view intelligence as a global construct composed of more-specific cognitive functions (e.g., auditory and visual–perceptual processing, spatial abilities, processing speed, and working memory). A useful definition of intellectual function is the capacity to think in the abstract, reason, problem solve and comprehend.

The expression of intellect is mediated by many factors, including language development, sensorimotor abilities, genetics, heredity, environment, and neurodevelopmental dysfunction or neuropathology. When an individual's intelligence is measured at a standard score of 70 or lower, and significant weaknesses in adaptive skills are indicated, consideration of the diagnosis of Intellectual Disability would be warranted. In DSM-5, the previous diagnostic term of Mental Retardation has been changed to Intellectual Disability. DSM-5 also includes the term Intellectual Developmental Disorder to indicate weaknesses in intellectual functioning that begin during the early developmental period (Chapter 36).

The clinical assessment of intellectual functioning has proved useful in identifying intellectual disability, informing treatment strategies, and in predicting future functionality (e.g., academic, occupational, and social). Notwithstanding, intelligence test scores (e.g., IQ) reflect only part of an individual's ability profile. Functionally, there are some common characteristics that distinguish children with deficient intellectual functioning from those with average or above average abilities. Typically, those at the lowest end of the spectrum (e.g., profound or severe intellectual deficiencies) are incapable of independent function, and require a highly structured environment with constant aid and supervision (see Chapter 36). At the other end of the spectrum are those with unusually well-developed intellect (e.g., gifted). Although this level of intellectual functioning offers many opportunities, it can also be associated with functional challenges related to socialization, learning style, and communication and perceptual differences. Individuals whose intellect falls in the below average range (sometimes referred to as the "borderline" or "slow learner" range) tend to experience greater difficulty processing and managing information that is abstract, making connections between concepts and ideas, and generalizing information (e.g., may be able to comprehend a concept in one setting but are unable to carry it over and apply it in different situation). In general, these individuals tend to do better when information is presented in more concrete and explicit terms, and when working with rote information (e.g., memorizing specific material). Stronger intellect is associated with better-developed concept formation, critical thinking, problem solving, understanding and formulation of rules, brainstorming and creativity, and metacognition (the ability to "think about thinking")

### Frontal Lobe Functioning

**Attention**

Most brain processes are heavily dependent on functional arousal, alertness, and attention. Any malfunction within or across these systems will likely cause some degree of breakdown in other cognitive processes. Functional attention subsumes intact neuroanatomic and neurochemical brain systems. Structurally, brain regions involved include subcortical, cortical, and association areas throughout the brain. Primary structures involved include brainstem regions (e.g., basal ganglia), the limbic system (e.g., amygdala and hippocampus), and the frontal lobes (e.g., prefrontal cortex). The neurotransmitter dopamine, along with its neuronal pathways, has been identified as a major chemical moderator of attention. It is through the cognitive mechanisms of attention and executive functions that the child’s brain acquires, organizes, and processes information. These mechanisms also allow the child to regulate, plan, and monitor their behaviors and thoughts. Children with attention dysfunction comprise a widely heterogeneous group who show various patterns of impairment of these systems (see Chapter 33). The resulting symptoms not only affect behavior, learning, and academic skills development, but also have an impact on the child’s emotional, social, and adaptive development and functioning.

Attention is far from a unitary, independent, or specific function. This may be illustrated best through the phenotype associated with Attention-Deficit/Hyperactivity Disorder (ADHD). ADHD is not only a disorder of impaired focus, but also includes a host of symptoms related to problems with vigilance, distractibility, impulsivity in thought and behavior, hyperactivity, and flexibility. Disordered attention can occur owing to faulty mechanisms in and/or across subdomains of attention. These subdomains include selective attention (the ability to focus attention to a particular stimulus and to discriminate relevant from irrelevant information), divided attention (the ability to orient to more than one stimulus at a given time), sustained attention (the ability to maintain one's focus), and alternating attention (the capacity to shift focus between stimuli).

Attention problems in school-age children can manifest at any point in the process, from arousal through output. Children with diminished alertness and arousal can exhibit signs of mental fatigue in a classroom or when engaged in any activity requiring sustained focus. They might yawn, stretch, fidget, and daydream. They can become overactive in an effort to attain or maintain a higher level of arousal. They are apt to have difficulty allocating and sustaining their concentration, and their efforts may be erratic and unpredictable, with extreme performance inconsistency. These children can also have difficulty discriminating between important and unimportant information. Such weaknesses of determining saliency often result in focusing on the wrong stimuli, at home, in school, and socially, and can result in the child's missing important information and can impede their ability to take notes, to summarize information, or to recognize what to study for a test. In the social context, poor attention may result in inept social interaction (e.g., because of factors such as not “hearing” what others say). Some children present with what has been termed sluggish cognitive tempo. Children with sluggish cognitive tempo have many inattentive features without a history of significant hyperactivity and/or impulsiveness. Some researchers believe that sluggish cognitive tempo may be a different disorder from ADHD, with its own characteristics, including hypoactivity, lethargy, confusion, and mental "fogginess.”
Distractibility can take the form of listening to extraneous noises instead of a teacher, staring out the window, or constantly thinking about the future. These children often show evidence of superficial concentration, where their level of focus is not of sufficient intensity to capture specific information. As a result, these children are often described as “forgetful” because directions and explanations need to be repeated and details (e.g., changes in operational signs in mathematics) may be missed. These children can also exhibit difficulties with cognitive activation and generalization, passively processing and not linking information with prior knowledge and experience, or overrelying on prior experience.

Attention dysfunction can affect the output of work, behavior, and/or social activity. These children have a tendency to perform or act without previewing a likely outcome or thinking through the potential consequences of what they are about to do or say. Their impulsivity can lead to careless mistakes in academic work and unintended misbehavior. It is important to appreciate that most children with attentional dysfunction also harbor other forms of neurodevelopmental dysfunction that can be associated with academic disorders (with some estimates suggesting up to 60% comorbidity).

**Executive Functioning**
There is considerable overlap between attention and executive functioning. Additions to the ICD classification system include a code for Frontal Lobe and Executive Function Deficit (799.55). Executive functioning is an umbrella term used to describe specific cognitive processes involved in regulating, guiding, organizing, and monitoring of thoughts and actions (cognitive, behavioral, and emotional functions) to achieve a specific goal. Processes considered to be executive in nature include inhibition control, flexibility (the ability to shift between activities or thoughts), emotional control, initiation skills, planning, organization, working memory, and self-monitoring.

Studies indicate that executive functioning can be strengthened in children as young as age 4 yr, which suggests that executive functioning is actively developing in the preschool-age child.

Executive function deficits that have particular impact on school function include inhibition, or inhibitory control, the ability to control a response, whether it be cognitive or behavioral. Children with inhibitory control deficits may answer questions prematurely and fail to check their work. Behaviorally, these children may speak without first considering the impact of what they say. In the social context, disinhibited children may interrupt others and demonstrate other impulsive behaviors that often interfere with interpersonal relationships (see Chapter 33).

The function of working memory has been the focus of significant research efforts. Working memory can be defined as the ability to hold, manipulate, and store information for short periods. In its simplest form, working memory involves the interaction of short-term verbal and visual processes (e.g., memory, phonologic awareness and spatial skills) with a centralized control mechanism that is responsible for coordinating all of the cognitive processes involved (e.g., temporarily suspending information in memory while working with it). Developmentally, working memory capacity can double or triple between the preschool years and adolescence. A child with working memory dysfunction might carry a number and then forget what it was that the child intended to do after carrying that number. Working memory is an equally important underlying function for reading, where it enables the child to remember the beginning of a paragraph when the child arrives at the end of it. In writing, working memory helps children remember what they intend to express in written form while they are performing another task, like placing a comma or working on spelling a word correctly. Working memory also enables the linkage between new incoming information in short-term memory with prior knowledge or skills held in longer-term memory (Table 32-1).

**Memory**
Memory is a term used to describe the cognitive mechanism by which information is acquired, retained, and recalled. Structurally, some major brain areas involved in memory processing include the hippocampus, the fornix, the temporal lobes, and the cerebellum, with connections in and between most brain regions. The memory system can be partitioned into subsystems based on processing sequences; the form, time span, and method of recall; whether memories are conscious or unconsciously recalled; and the types of memory impairments that can occur.

Once information has been identified (through auditory, visual, tactile, and/or other sensory processes), it needs to be encoded and registered, a mental process that constructs a representation of the information into the memory system. The period of time (typically seconds) during which this information is being held and/or manipulated for registration, and ultimately encoded, consolidated, and retained, is referred to as working memory (see above). Other descriptors include short-term memory and immediate memory. Consolidation and storage represent the process by which information in short-term memory is transferred into long-term memory. Information in long-term memory can be available for hours or as long as a lifetime. Long-term memories are generally thought to be housed, in whole or in part, in specific brain regions (e.g., the cortex, cerebellum). Ordinarily, consolidation in long-term memory is accomplished in 1 or more of 4 ways: pairing 2 bits of information (such as a group of letters and the English sound it represents); storing procedures (consolidating new skills, such as the steps in solving mathematics problems); classifying data in categories (filing all insects together in memory); and linking new information to established rules, patterns, or systems of organization (rule-based learning).

Once information finds its way into long-term memory, it must be accessed. In general, information can be retrieved spontaneously (a process known as free recall) or with the aid of cues (cued or recognition recall). Some other common descriptors of memory include anterograde memory (the capacity to learn from a single point in time

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**Table 32-1 Symptom Expression of Executive Function Deficit**

<table>
<thead>
<tr>
<th>EXECUTIVE FUNCTION DEFICIT</th>
<th>SYMPTOM EXPRESSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disinhibition</td>
<td>Impulsivity/poor behavioral regulation</td>
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<tr>
<td></td>
<td>Interrupts</td>
</tr>
<tr>
<td></td>
<td>“Blurts” things out</td>
</tr>
<tr>
<td>Shifting</td>
<td>Problems with transitioning from one task/activity to another</td>
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<tr>
<td></td>
<td>Unable to adjust to unexpected change</td>
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<tr>
<td></td>
<td>Repeats unsuccessful problem-solving approaches</td>
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<tr>
<td>Initiation</td>
<td>Difficulty independently beginning tasks/activities</td>
</tr>
<tr>
<td></td>
<td>Lacks initiative</td>
</tr>
<tr>
<td></td>
<td>Difficulty developing ideas or making decisions</td>
</tr>
<tr>
<td>Working memory</td>
<td>Challenges following multistep instruction (e.g., only completes 1 of 3 steps)</td>
</tr>
<tr>
<td></td>
<td>Forgetfulness</td>
</tr>
<tr>
<td>Organization and planning</td>
<td>Fails to plan ahead</td>
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<tr>
<td></td>
<td>Work is often disorganized</td>
</tr>
<tr>
<td></td>
<td>Procrastinates and does not complete tasks</td>
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<tr>
<td></td>
<td>“Messy” child</td>
</tr>
<tr>
<td>Self-monitoring</td>
<td>Fails to recognize errors and check work</td>
</tr>
<tr>
<td></td>
<td>Does not appreciate impact of actions on others</td>
</tr>
<tr>
<td></td>
<td>Poor self-awareness</td>
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<tr>
<td>Affect control</td>
<td>Experiences behavioral and emotional outbursts (e.g., tantrums)</td>
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<tr>
<td></td>
<td>Easily upset/frustrated</td>
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<td></td>
<td>Frequent mod changes</td>
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</table>
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forward), retrograde memory (the capacity to recall information that was already learned), and explicit memory (conscious awareness of recall), implicit memory (subconscious recall: no awareness that the memory system is being activated), procedural memory (memory for how to do things), and prospective memory or remembering to remember.

As children proceed through school, the demands for the efficient use of memory progressively increase. By secondary school, rapid and precise recall is heavily emphasized. Children can have trouble with 1 or more memory mechanisms. They might struggle with the initial registration of information in short-term memory. Others might have difficulty storing newly introduced information. Other children might have difficulty accessing (retrieving) information, despite having registered and stored it effectively. Children can experience frustration in their efforts at consolidating information into long-term memory and/or encounter difficulty with simultaneous recall (retrieval of several facts or procedures at once). Some students exhibit delayed automatization: not enough of what they have learned in the past is accessible to them instantaneously and with no expenditure of effort. Such skills as forming letters, mastering mathematical facts, and decoding words must ultimately become automatic if students are to make good academic progress.

Weaknesses with memory processing can be highly specific and/or dependent on the material. Some children struggle to learn visual-spatial material, whereas others may be deficient in learning auditory information. Some have difficulty processing linear data or sequential information. Some can experience difficulty with rote data (e.g., word lists) yet have little or no difficulty registering information in context (e.g., a narrative). Although in-depth examination (e.g., neuropsychological testing) is often necessary to differentiate potential memory weaknesses and their impact on the child’s overall functioning, screening for memory problems should be part of any well-child examination.

Social Cognition

For the school-age child, the development and effective use of social skills is of immeasurable importance. It is heavily dependent on secure social cognition, which is composed of mental processes that allow an individual to understand and interact with the social environment. Although some evidence shows that social cognition exists as a discrete area of neurodevelopmental function, multiple cognitive processes are involved with social cognition. These include the ability to recognize, interpret, and make sense of the thoughts, communications (verbal and nonverbal), and actions of others, the ability to understand that others’ perceptions, perspectives, and intentions might differ from our own (commonly referred to as “theory of mind”), the ability to use language to communicate with others socially (pragmatic language), and the ability to make inferences about others and/or the environment based on contextual information. It can also be argued that social cognition involves processes associated with memory and executive functions like flexibility.

CLINICAL MANIFESTATIONS

School-age children with neurodevelopmental dysfunctions vary widely with regard to clinical presentations. Their specific patterns of academic performance and behavior represent formal common pathways, the convergence of many forces, including interacting cognitive strengths and deficits; environmental, social, or cultural factors; temperament; educational experience; and intrinsic resilience (Table 32-2). Symptoms of academic disorders differ with age. Children in preschool or kindergarten might present with delayed language development, including problems with articulation, vocabulary development, word finding and rhyming. They often experience early challenges with learning colors, shapes, letters and numbers, the alphabet, and days of the week. Difficulty following instructions, overactivity, and distractibility may be early symptoms of emerging attention and inhibitory control weaknesses. Difficulties with fine motor development (e.g., grasping crayons and pencils, coloring or drawing) and social interaction are not uncommon. As these children enter elementary school, they can evidence problems integrating and associating letters and sounds and problems with semantic knowledge such as mixing up their words (like go and eat). While learning to read and spell, challenges with reversals (b/d), inversions (m/w), transpositions (felt/left), and substitutions (house/home) might persist. Reading comprehension may be weak.

Children with early signs of a mathematics weakness might have difficulty with concepts of quantity or with adding or subtracting without using concrete representation (e.g., their fingers when calculating). Difficulty learning time concepts and confusion with directions (left/right) might also be observed. Sequencing problems are noted in reading, spelling and writing, and mathematics. Poor fine motor control and coordination and poor planning can lead to spelling and writing problems. Attention and behavioral regulation weaknesses observed earlier can continue, and together with executive functioning weaknesses (e.g., organization, initiation skills), further complicate the child’s ability to acquire and generalize new knowledge.

Middle school brings with it a significant shift in cognitive, academic, and regulatory demands, as children in this age group are expected to be increasingly independent, causing further difficulties for a child with existing attention, inhibitory, and/or executive challenges. In reading and writing, middle school children might present with transposition and sequencing errors; might struggle with root words, prefixes, and suffixes; might have difficulty with written expression; and might avoid reading and writing altogether. Challenges completing word problems in math are common. Difficulty with recall of information might also be experienced. Although observable in both lower and more advanced grades, behavioral, emotional, and/or social difficulties tend to become more salient in middle school children who experience cognitive and/or academic problems.

Many of these challenges continue well into high school. High school students can present with deficient reading comprehension, written expression, and slower processing efficiency. Trouble answering

<table>
<thead>
<tr>
<th>Table 32-2</th>
<th>Neurodevelopmental Dysfunction Underlying Academic Disorders</th>
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<tr>
<td><strong>ACADEMIC DISORDER</strong></td>
<td><strong>POTENTIAL UNDERLYING NEURODEVELOPMENTAL DYSFUNCTION</strong></td>
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<td><strong>Reading</strong></td>
<td>Language</td>
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<td></td>
<td>• Phonologic processing</td>
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<td>• Verbal fluency</td>
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<td>• Syntactic and semantic skills</td>
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<td><strong>Memory</strong></td>
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<td>• Working memory</td>
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<td><strong>Sequencing</strong></td>
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<td><strong>Visual–spatial Attention</strong></td>
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<td><strong>Written expression, spelling</strong></td>
<td>Language</td>
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<td></td>
<td>• Phonologic processing</td>
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<td>• Syntactic and semantic skills</td>
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<td></td>
<td><strong>Graphomotor</strong></td>
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<td></td>
<td><strong>Visual–spatial Attention</strong></td>
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<td><strong>Mathematics</strong></td>
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<td><strong>Working memory</strong></td>
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<td><strong>Language</strong></td>
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<td><strong>Sequencing</strong></td>
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<td><strong>Graphomotor</strong></td>
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<td></td>
<td><strong>Attention</strong></td>
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</table>

Isolated neurodevelopmental dysfunction can lead to a specific academic disorder, but more often there is a combination of factors underlying weak academic performance. In addition to the dysfunction in neurodevelopmental domains listed in the table, the clinician must also consider the possibility of limitations of intellectual and cognitive abilities or associated social and emotional problems.
open-ended questions, dealing with abstract information, and producing executive control (e.g., self-monitoring, organization, planning, and self-starting) is often reported.

Reading
Reading disorders (see Chapter 34), also termed dyslexia, can stem from any number of neurodevelopmental dysfunctions as described earlier (see Table 32-2). Most commonly, language and/or auditory processing weaknesses are present as evidenced by poor phonologic processing. Challenges with phonologic processing often result in deficiticiencies at the level of decoding individual words and, consequently, a delay in automaticity (e.g., acquiring a repertoire of words they can identify instantly) that causes reading to be slow, laborious, and frustrating. Without effective identification and intervention, reading comprehension, and ultimately the acquisition of knowledge may be seriously compromised. Deficits in other core neurodevelopmental domains might also be present. Weak working memory might make it difficult for a child to hold sounds and/or symbols in mind while breaking down words into their component sounds or might cause reading comprehension problems. Some children experience temporal-ordering weaknesses and struggle with reblending phonemes into correct sequences. Memory dysfunction can cause problems with recall and summarization of what was read. Some children with higher-order cognitive deficiencies have trouble understanding what they read because they lack a strong grasp of the concepts in a text. Although relatively rare as a cause of reading difficulty, problems with visual–spatial functions (e.g., visual perception) can cause children difficulty in recognizing letters. It is not unusual for children with reading problems to avoid reading practice, and a delay in reading proficiency becomes increasingly pronounced and difficult to remediate.

Spelling and Writing
Spelling and writing impairments share many related underlying processing deficits with reading, so it is not surprising that the 2 disorders often occur simultaneously in school-age children (see Table 32-2). Core neurodevelopmental weaknesses can include phonologic and decoding difficulties, orthographic problems (coding letters and words into memory), and morphologic deficits (use of suffixes, prefixes, and root words). Problems in these areas can manifest as phonetically poor, yet visually comparable approximations to the actual word (fight for fight), spelling that is phonetically correct but visually incorrect (fite for fight), and inadequate spelling patterns (played as plade). Children with memory disorders might misspell words because of coding weaknesses. Others misspell because of poor auditory working memory that interferes with their ability to process letters. Sequencing weaknesses often result in transposition errors when spelling. Overall, the careful analysis of a child’s errors can provide valuable insights into the nature of their spelling problems. As children proceed through school, demands increase for large amounts of well-organized written output.

Writing difficulties have been classified as disorder of written expression, or dysgraphia (see Table 32-2). Although many of the same dysfunctions described for reading and spelling can contribute to problems with writing, written expression is the most complex of the language arts, requiring synthesis of many neurodevelopmental functions (e.g., auditory, visual–spatial, memory, executive). Deficits in any of these domains can be problematic. Even when a child’s phonologic and/or orthographic skills are functional, the child can experience writing problems owing to weaknesses with language, attention, sequencing and/or fine motor development. These weaknesses can occur in written output that is difficult to comprehend, disjointed, and/or poorly organized. The child with working memory challenges can lose track of what the child intended to write. Attention deficits can make it hard for a child to mobilize and sustain the mental effort, pacing, and self-monitoring demands necessary for writing. In many cases, writing is laborious because of an underlying graphomotor dysfunction (e.g., fluency does not keep pace with ideation and language production). Thoughts may also be forgotten or underdeveloped during writing because the mechanical effort is so taxing.

Mathematics
Delays in mathematical ability, known as mathematics disorder or dyscalculia, can be especially refractory to correction, partly because math involves the assimilation of both procedural knowledge (e.g., calculations) and higher-order cognitive processes (e.g., working memory) (see Table 32-2). A school-based study found that no student who was delayed for longer than 6 mo in mathematics in 6th grade ever caught up; another study found persistence of severe arithmetic disorder in half of affected preteen children. Factors associated with persistence of difficulties included the disorder’s severity and heritability. Significant mathematical weaknesses can become virtually insurmountable because the subject is so cumulative in its structure.

Some children experience mathematics failure because of weaknesses in reasoning and problem solving (e.g., intellectual functioning). It may be hard for them to grasp and apply concepts effectively and/or systematically. Good mathematicians are able to use both verbal and perceptual conceptualization to understand such concepts as fractions, percentages, equations, and proportion. Children with language dysfunctions have difficulty in mathematics because they have trouble understanding their teachers’ verbal explanations of quantitative concepts and operations and are likely to experience frustration in solving word problems and in processing the vast network of technical vocabulary in math. Mathematics also relies on visualization. Children who have difficulty forming and recalling visual imagery may be at a disadvantage in acquiring mathematical skills. They might experience problems writing numbers correctly, placing value locations, and processing geometric shapes or fractions. Children with attention, inhibitory control, or executive deficits (e.g., working memory) may be unable to focus on fine detail (such as operational signs), might take an impulsive approach to problem solving, engage in little or no self-monitoring, forget components of the same problem, or commit careless errors. When a child’s memory system is weak, the child might have difficulty recalling appropriate procedures and automatizing mathematical facts (e.g., multiplication tables). Moreover, it is not unusual for children with mathematical disabilities to have superimposed mathematics phobias. Anxiety over mathematics can be especially debilitating.

Nonacademic Problems
Neurodevelopmental dysfunctions commonly have effects that extend far beyond academic performance. These effects may be related to the dysfunctions themselves or to secondary sequelae (e.g., persistent failure and frustration). The impulsivity and lack of effective self-monitoring of children with attention and impulse-control deficits can lead to unacceptable actions that were unintentional. Children with neurodevelopmental dysfunctions can experience excessive performance anxiety or clinical depression, and sadness, self-deprecatory comments, declining self-esteem, chronic fatigue, loss of interests, and even suicidal ideation can ensue. Some children lose motivation. They tend to give up and exhibit learned helplessness, a sense that they have no control over their destiny. Therefore, they feel no need to exert effort and develop future goals. These children may be easily led toward dysfunctional interpersonal relationships, detrimental behaviors (e.g., delinquency), and the development of mental health and personality disorders, such as mood disorders (see Chapter 26) or antisocial personality disorder.

ASSESSMENT AND DIAGNOSIS
The primary care pediatrician has a critical role in identifying and evaluating the child with an academic disorder. A system of screening and surveillance should be incorporated into routine office visits to promote early identification of academic difficulties. The pediatrician should be aware of a family medical history that includes a parent who still struggles with reading or time management, or an older sibling who has failed at school. Factors in the child’s medical history should be flagged, such as extreme prematurity or chronic medical conditions. Children with low birthweight and those born prematurely who appear to have been spared more serious neurologic problems might only manifest academic problems later in their school career and they
warrant particular attention. Children falling into these high risk categories should be flagged for an increased level of scrutiny at routine well-child visits as well as acute-care visits, especially if physical complaints are nonspecific. There should be a low threshold for initiating further school performance screening and assessment of these children. Warning signs might be subtle or absent and problems will not be recognized unless there is a system of eliciting and identifying school problems as part of the routine well-child visit. Parents might have concerns about their child’s learning progress but be reluctant to share these with the pediatrician unless prompted such as through completion of a standard developmental screening questionnaires or direct questioning of parents regarding possible concerns about their child’s school performance. Inconsistency in report from grade to grade may sometimes be caused by a difference in teaching styles or classroom demands. The type of deficit will also be influential; for example, problems with basic phonemic awareness would be more apparent earlier, while reading comprehension difficulties would emerge later.

Review of school report cards can provide useful clues to patterns of neurodevelopmental dysfunction. In addition to the patterns of grades in the various academic skill areas, it is also important to review ratings of classroom behavior, sometimes listed under headings such as deportment, behavior, conduct, effort/work habits, or citizenship. Review of standardized testing is helpful, and poor scores could be caused by a learning disorder, ADHD, anxiety, lack of motivation, or some combination thereof. Conversely, above-average scores tend to rule out learning or attention problems, but motivation or adjustment issues could then explain a discrepancy between standardized scores and classroom performance. Comparison of how long the homework should take, and how long it takes the child is recommended. Children with ADHD, learning disorders, or emotional/behavioral issues often find homework to be a contentious activity.

The primary care physician is responsible for identifying or ruling out any underlying or associated medical problems that could be impeding the academic performance of the patient who is struggling in school. Vision and hearing screening are critical components of the medical evaluation and any suspicion of sensory difficulty should warrant referral for more definitive testing. The influence of chronic medical problems or potential side effects of medications should be considered. Sleep deprivation is increasingly being recognized as a contributor to academic problems and the possibility of substance abuse must always be a consideration, especially in the adolescent who was previously achieving well at school and has manifested a rapid decline in academic performance.

The physician should be alert for dysmorphic physical features, minor congenital anomalies, or constellations of physical findings (such as cardiac anomalies and palatal anomalies in velocardiofacial syndrome) and should perform a detailed neurologic examination. Special investigations, such as electroencephalograms or brain scans, are not indicated in the absence of specific medical findings. Measures of brain function, such as functional MRI, offer insight into possible areas of neurodevelopmental dysfunction, but they largely remain only research tools with limited application in the general clinical setting at this time.

If problems emerge, the pediatrician should address medical causes or associated conditions. The pediatrician can advise and assist parents in obtaining necessary psychoeducational and/or emotional evaluations through the school or by referral to independent clinicians.

Those physicians with a particular interest in learning disorders can extend their participation in the evaluation process. They can obtain data on neurodevelopmental function through the use of questionnaires completed by the parents, the school, and (if old enough) the child, providing information about behavioral adjustment, patterns of academic performance, and traits associated with specific developmental dysfunctions. Screening instruments such as the Pediatric Symptom Checklist and standardized behavioral questionnaires, including the Child Behavior Checklist (CBCL) and the Behavior Assessment System for Children—Second Edition (RASC-2) can aid in evaluation (see Chapter 20).

The physician may also perform an extended neurologic and developmental assessment. Available pediatric neurodevelopmental examination instruments that facilitate direct sampling of various neuropsychologic functions, such as attention, memory, and language, include the Pediatric Early Elementary Examination (PEEX II) and the Pediatric Examination of Educational Readiness at Middle Childhood (PEERAMID II). Examinations of this type also include direct behavioral observations and assessment of minor neurologic indicators (sometimes called soft signs). The latter include various associated movements and other phenomena often associated with neurodevelopmental dysfunction.

A child who is functioning poorly during the school years usually requires a multidisciplinary evaluation, including a pediatrician, a psychologist, and, if possible, a psychoeducational specialist (sometimes called an educational diagnostician) who can undertake a detailed analysis of academic skills and subskills. Other professionals should become involved, as needed, in individual cases, such as a speech-language pathologist, an occupational therapist, a neurologist, and a social worker. In some cases, more in-depth examination of a child’s neurocognitive status is warranted. This is particularly true for children who present with developmental or cognitive difficulties in the presence of a medical condition (e.g., epilepsy, traumatic brain injury, childhood cancers/brain tumors, genetic conditions). A neuropsychologic evaluation involves comprehensive assessment of brain function as a means of understanding brain function across domains. The goal of neuropsychologic assessment is to understand brain function via identification of a child’s profile of cognitive strengths and weaknesses. Neuropsychologic data are often analyzed together with other tests (e.g., structural), such as MRIs, to look for supporting evidence of any areas of difficulty (e.g., memory weaknesses associated with temporal lobe anomalies).

Many children undergo evaluations in school. Such assessments are guaranteed in the United States under Public Law 101-476, the IDEA. In addition, children found to have attentional dysfunction and other disorders might qualify for educational accommodations under Section 504 of the Rehabilitation Act of 1973.

Multidisciplinary evaluations conducted in schools are usually very helpful, but they are focused primarily on determining whether a student meets the eligibility criteria for special education services. School budgeting constraints or lack of personnel can also affect the quality of evaluations and the extent of recommended services. Many parents seek independent evaluations or second opinions outside of the school setting, and pediatricians can facilitate such outside assessments.

Psychoeducational testing can yield relevant data, especially when such assessments include careful analyses that pinpoint where breakdowns are occurring in the processes of reading, spelling, writing, and mathematics. Input from multiple sources can be used in formulating specific recommendations for regular and special educational teachers and for interventions that can be implemented at home. A mental health specialist can be valuable in identifying family-based issues or psychiatric disorders that may be complicating or aggravating neurodevelopmental dysfunctions.

**TREATMENT**

There are a number of standard approaches that should be incorporated into any management plan for a student who is struggling academically. The primary physician can play an important role as a consultant in overseeing and monitoring the implementation of these steps. Management of children with neurodevelopmental dysfunctions often needs to be multidisciplinary. Most children require several of the following forms of intervention.

**Demystification**

Many children with neurodevelopmental dysfunctions have little or no understanding of the nature or sources of their academic difficulties. Once an appropriate descriptive assessment has been performed, it is important to explain to the child the nature of the dysfunction while delineating the child’s strengths. This explanation should be provided
in nontechnical language, communicating a sense of optimism and a desire to be helpful and supportive.

**Bypass Strategies (Accommodations)**
Numerous techniques can enable a child to circumvent neurodevelopmental dysfunctions. Such bypass strategies are ordinarily used in the regular classroom. Examples of bypass strategies include using a calculator while solving mathematical problems, writing essays with a word processor, presenting oral instead of written reports, solving fewer mathematical problems, being seated near the teacher to minimize distraction, presenting correctly solved mathematical problems visually, and taking standardized tests untimed. These bypass strategies do not cure neurodevelopmental dysfunctions, but they minimize their academic and nonacademic effects and can provide a scaffold for more successful academic achievement.

**Interventions (Remediation of Skills)**
Interventions can be implemented at home and in school to strengthen the weak links in academic skills. Reading specialists, mathematics tutors, and other such professionals can use diagnostic data to select techniques that use a student's neurodevelopmental strengths in an effort to improve decoding skills, writing ability, or mathematical computation skills. Remediation need not focus exclusively on specific academic areas. Many students need assistance in acquiring study skills, cognitive strategies, and productive organizational habits.

Early identification is critical so that appropriate instructional interventions can be introduced in an effort to minimize the long-term effects of academic disorders. Any interventions should be empirically supported (e.g., phonologically based reading intervention has been shown to significantly improve reading skills in school-age children). Remediation may take place in a resource room or learning center at school and is usually limited to children who have met the educational criteria for special education resource services as described earlier.

Interventions that can be implemented at home could include drills to aid the automatization of subskills, such as arithmetic facts or letter formations, or the use of phonologically based reading programs.

There are a number of treatment/intervention approaches to strengthening executive function that have demonstrated positive findings. These include computerized training programs such as CogMed (Pearson) that has been demonstrated to strengthen working memory skills in children via a computer game model. Curriculum-based classroom programs, such as the Tools of the Mind (Tools) and PATHS (Promoting Alternative Thinking Strategies) also have accumulating research support. These programs employ approaches such as social play and target areas such as self-control and problem-solving to teach and strengthen executive functions. Aerobic exercise and martial arts such as Tae Kwon Do, which stresses discipline and emphasizes the development of self-regulation (e.g., impulse control), have demonstrated improvements that generalize in many aspects of executive functions and attention.

**Developmental Therapy**
Controversy exists about the efficacy of treatments to enhance weak developmental functions. Nevertheless, some forms of developmental therapy are widely accepted. Speech-language pathologists commonly offer intervention for children with various forms of language disability. Occupational therapists strive to improve the motor skills of certain students with writing problems, and physical therapists address gross motor clumsiness.

**Curriculum Modifications**
Many children with neurodevelopmental dysfunctions require alterations in the school curriculum to succeed, especially as they progress through secondary school. Students with memory weaknesses might need to have their courses selected for them so that they do not have an inordinate cumulative memory load in any single semester. The timing of foreign language learning, the selection of a mathematics curriculum, and the choice of science courses are critical issues for many of these struggling adolescents.

**Strengthening of Strengths**
Affected children need to have their affinities, potentials, and talents identified clearly and exploited widely. It is as important to augment strengths as it is to attempt to remedy deficiencies. Athletic skills, artistic inclinations, creative talents, and mechanical abilities are among the potential assets of certain students who are underachieving academically. Parents and school personnel need to create opportunities for such students to build on these assets and to achieve respect and praise for their efforts. These well-developed personal assets can ultimately have implications for the transition into young adulthood, including career or college selection.

**Individual and Family Counseling**
When academic difficulties are complicated by family problems or identifiable psychiatric disorders, psychotherapy may be indicated. Clinical psychologists or child psychiatrists may offer long- or short-term therapy. Such intervention may involve the child alone or the entire family. Cognitive-behavioral therapy is a technique that is increasingly popular. It is essential that the therapist have a firm understanding of the nature of a child's neurodevelopmental dysfunctions.

**Controversial Therapies**
A variety of treatment methods for neurodevelopmental dysfunctions have been proposed that currently have no known scientific evidence base of efficacy. This list includes dietary interventions (vitamins, elimination of food additives or potential allergens), neuromotor programs or medications to address vestibular dysfunction, eye exercises, filters, tinted lenses, and various technologic devices. Parents should be cautioned against expending the excessive amounts of time and financial resources usually demanded by these remedies. In many cases, it is difficult to distinguish the nonspecific beneficial effects of increased support and attention paid to the child from the supposed target effects of the intervention.

**Medication**
Psychopharmacologic agents may be especially helpful in lessening the toll of neurodevelopmental dysfunctions. Most commonly, stimulant medications are used in the treatment of children with attention deficits. Although most children with attention deficits have other associated dysfunctions (such as language disorders, memory problems, motor weaknesses, or social skill deficits), medications such as methylphenidate, dextroamphetamine, lisdexamfetamine, mixed amphetamine salts, and atomoxetine can be important adjuncts to treatment by helping some children focus more selectively and control their impulsivity. When depression or excessive anxiety is a significant component of the clinical picture, antidepressants or antianxiety drugs may be helpful. Other drugs may improve behavioral control (see Chapter 21). Children receiving medication need regular follow-up visits that include a history to check for side effects, a review of current behavioral checklists, a complete physical examination, and appropriate modifications of the medication dose. Periodic trials off medication are recommended to establish whether the medication is still necessary.

*Bibliography is available at Expert Consult.*
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Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood and one of among the most prevalent chronic health conditions affecting school-age children. ADHD is characterized by inattention, including increased distractibility and decreased self-inhibitory capacity; and motor overactivity and motor restlessness (Table 33-1). Definitions vary in different countries (Table 33-2). Affected children commonly experience academic underachievement, problems with interpersonal relationships with family members and peers, and low self-esteem. ADHD often co-occurs with other emotional, behavioral, language, and learning disorders (Table 33-3). For 40-50% of affected children, the disorder appears to continue with varying manifestations into adulthood, and leads to significant under- and unemployment, social dysfunction, and an increased risk of antisocial behaviors including substance abuse, difficulties maintaining relationships, and encounters with the law.

**ETIOLOGY**

ADHD may be a final common pathway for a variety of complex brain developmental processes. Mothers of children with ADHD are more likely to experience birth complications, such as toxemia, lengthy labor, and complicated delivery. Maternal drug use, smoking and alcohol use during pregnancy, lead or mercury exposure (prenatal or postnatal) are commonly linked to attentional difficulties associated with the development of ADHD. Food colorings and preservatives have inconsistently been associated with hyperactivity in previously hyperactive children.

There is a very strong genetic component to ADHD. Genetic studies have primarily implicated at least 2 candidate genes, the dopamine transporter gene (DAT1) and a particular form of the dopamine 4 receptor gene (DRD4), in the development of ADHD. Additional genes that might contribute to ADHD include DOCK2 associated with a pericentric inversion 46N inv(3)(p14:q21) involved in cytokine regulation, a sodium-hydrogen exchange gene, other dopaminergic genes (DRD5), serotonergic genes (5HTT, HTR1B), and the synaptosomal-associated protein, SNAP-25.

Abnormal brain structures are linked to an increased risk of ADHD; 20% of children with severe traumatic brain injury are reported to have subsequent onset of substantial symptoms of impulsivity and inattention. Children with head or other injury and in whom ADHD is later diagnosed might have impaired balance or impulsive behavior as part of the ADHD, thus predisposing them to injury. Structural and functional abnormalities have been identified in children with ADHD without preexisting identifiable brain injury. These include dysregulation of the frontal subcortical circuits, small cortical volumes in this region, widespread small-volume reduction throughout the brain, and abnormalities of the cerebellum, particularly midline/vermian elements. Abnormalities in neural networks or circuits have been identified with functional MRI.

Psychosocial family stressors can also contribute to or exacerbate the symptoms of ADHD, including poverty, exposure to violence, and under- or malnutrition.

**EPIDEMIOLOGY**

Studies of the prevalence of ADHD across the globe have generally reported that 9% of school-age children are affected, although rates vary considerably by country, perhaps partly as a result of differing sampling and testing techniques. Rates may be higher if symptoms (inattention, impulsivity, hyperactivity) are considered in the absence of functional impairment. The prevalence rate in adolescent samples is 2-6%. Approximately 2% of adults have ADHD. ADHD is often under-diagnosed in children and adolescents. Youth with ADHD are often undertreated with respect to what is known about the needed and appropriate doses of medications. Many children with ADHD also present with comorbid neuropsychiatric diagnoses, including opposition defiant disorder, conduct disorder, learning disabilities, depression, and anxiety disorders. The incidence of ADHD appears increased in children with neurologic disorders such as epilepsies, neurofibromatosis, tuberous sclerosis (see Table 33-3).

**PATHOGENESIS**

MRI studies indicate that a loss of normal asymmetry in the brain, in addition to smaller brain volumes of specific structures, such as the prefrontal cortex and basal ganglia, is seen in the brains of children with ADHD. Children with ADHD have approximately a 5-10% reduction in the volume of these brain structures. Functional MRI findings suggest low blood flow to the striatum. Functional MRI data also suggest deficits in a widespread functional networks for selective and tonic attention in ADHD, that include the striatum, prefrontal regions, parietal lobe, and temporal lobe. The prefrontal cortex and basal ganglia are rich in dopamine receptors. This knowledge, plus data about the dopaminergic mechanisms of action of medication treatment for ADHD, has led to the dopamine hypothesis, which postulates that disturbances in the dopamine system may be related to the onset of ADHD. Fluorodopa positron emission tomography scans also support the dopamine hypothesis through the identification of low levels of dopamine activity in adults.

**CLINICAL MANIFESTATIONS**

Development of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria leading to the diagnosis of ADHD occurred mainly in field trials with children 5-12 yr of age. Fewer studies utilizing Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria are available, but those that are available suggest a good correlation with data from DSM-IV criteria-based studies, despite the broadened age-based definition for onset of symptoms in DSM-5 (see Table 33-1). The current DSM-5 criteria state that the behavior must be developmentally inappropriate (substantially different from that of other children of the same age and developmental level), must begin before age 12 yr, must be present for at least 6 mo, must be present in 2 or more settings and reported as such by independent observers, and must not be secondary to another disorder. DSM-5 identifies 3 subtypes of ADHD. The first subtype, ADHD, predominantly inattentive type, often includes cognitive impairment and is more common in females. The other 2 subtypes, ADHD, predominately hyperactive-impulsive type, and ADHD, combined type, are more commonly diagnosed in males. Clinical manifestations of ADHD may change with age. The symptoms may vary from motor restlessness and aggressive and disruptive behavior, which are common in preschool children, to disorganized, distractible, and inattentive symptoms, which are more typical in older adolescents and adults. ADHD is often difficult to diagnose in preschoolers because distractibility and inattention are may be considered developmental norms during this period.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**

A diagnosis of ADHD is made primarily in clinical settings after a thorough evaluation, including a careful history and clinical interview to rule in or to identify other causes or contributing factors; completion of behavior rating scales by different observers from at least 2 settings (e.g., teacher and parent); a physical examination; and any necessary or indicated laboratory tests which arise from conditions suspected based on history and/or physical examination. It is important to systematically gather and evaluate information from a variety of sources, including the child, parents, teachers, physicians, and, when appropriate, other caretakers, over the course of both diagnosis and subsequent management.
**Table 33-1 | DSM-5 Diagnostic Criteria for Attention-Deficit/Hyperactivity Disorder**

**DIAGNOSTIC CRITERIA**

1. A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by (1) and/or (2):
   - **Inattention:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
     - **Note:** The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.
     1. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate).
     2. Often has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during lectures, conversations, or lengthy reading).
     3. Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction).
     4. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily sidetracked).
     5. Often has difficulty organizing tasks and activities (e.g., difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines).
     6. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers).
     7. Often loses things necessary for tasks or activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
     8. Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts).
     9. Is often forgetful in daily activities (e.g., doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments).
   - **Hyperactivity and impulsivity:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
     - **Note:** The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.
     1. Often fidgets with or taps hands or feet or squirms in seat.
     2. Often leaves seat in situations when remaining seated is expected (e.g., leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place).
     3. Often runs about or climbs in situations where it is inappropriate. (Note: In adolescents or adults, may be limited to feeling restless.)
     4. Often unable to play or engage in leisure activities quietly.
     5. Is often “on the go,” acting as if “driven by a motor” (e.g., is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with).
     6. Often talks excessively.
     7. Often blurts out an answer before a question has been completed (e.g., completes people’s sentences; cannot wait for turn in conversation).
     8. Often has difficulty waiting his or her turn (e.g., while waiting in line).
     9. Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may start using other people’s things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).
   2. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.
   3. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g., at home, school, or work; with friends or relatives; in other activities).
   4. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.
   5. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

Specify whether:
- **Combined presentation:** If both Criterion A1 (inattention) and Criterion A2 (hyperactivity-impulsivity) are met for the past 6 months.
- **Predominantly inattentive presentation:** If Criterion A1 (inattention) is met but Criterion A2 (hyperactivity-impulsivity) is not met for the past 6 months.
- **Predominantly hyperactive/impulsive presentation:** If Criterion A2 (hyperactivity-impulsivity) is met and Criterion A1 (inattention) is not met for the past 6 months.

Specify if:
- **In partial remission:** When full criteria were previously met, fewer than the full criteria have been met for the past 6 months, and the symptoms still result in impairment in social, academic, or occupational functioning.

Specify current severity:
- **Mild:** Few, if any, symptoms in excess of those required to make the diagnosis are present, and symptoms result in no more than minor impairments in social or occupational functioning.
- **Moderate:** Symptoms or functional impairment between “mild” and “severe” are present.
- **Severe:** Many symptoms in excess of those required to make the diagnosis, or several symptoms that are particularly severe, are present, or the symptoms result in marked impairment in social or occupational functioning.

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**Clinical Interview and History**

The clinical interview allows a comprehensive understanding as to whether the symptoms meet the diagnostic criteria for ADHD. During the interview, the clinician should gather information pertaining to the history of the presenting problems, the child’s overall health and development, and the social and family history. The interview should emphasize factors that might affect the development or integrity of the central nervous system or reveal chronic illness, sensory impairments, or medication use that might affect the child’s functioning. Disruptive social factors, such as family discord, situational stress, and abuse or neglect, can result in hyperactive or anxious behaviors. A family history of 1st-degree relatives with ADHD, mood or anxiety disorders, learning disability, antisocial disorder, or alcohol or substance abuse might indicate an increased risk of ADHD and/or comorbid conditions.

Behavior Rating Scales

Behavior rating scales are useful in establishing the magnitude and pervasiveness of the symptoms, but are not sufficient alone to make a diagnosis of ADHD. There are a variety of well-established behavior rating scales that have obtained good results in discriminating between children with ADHD and control subjects. These measures include, but are not limited to, the Vanderbilt ADHD Diagnostic Rating Scale; the Conner Rating Scales (parent and teacher); the ADHD Index; the Swanson, Nolan, and Pelham Checklist (SNAP); and the ADD-H: Comprehensive Teacher Rating Scale (ACTeRS). Other broadband checklists, such as the Achenbach Child Behavior Checklist (CBCL) or Behavioral Assessment Scale for Children (BASC), are useful, particularly in instances where the child may be experiencing co-occurring problems in other areas (anxiety, depression, conduct problems). Some, such as the BASC, include a validation scale to help determine the reliability of a given observer’s assessment of the child.

Physical Examination and Laboratory Findings

There are no standard laboratory tests available to identify ADHD in children. The presence of hypertension, ataxia, or a thyroid disorder should prompt further diagnostic evaluation. Impaired fine motor movement and poor coordination and other subtle neurologic motor signs (difficulties with finger tapping, alternating movements, finger-to-toe, skipping, tracing a maze, cutting paper) are common, but they are not sufficiently specific to contribute to a diagnosis of ADHD. The clinician should also identify any possible vision or hearing problems. The clinician should consider testing for elevated lead levels in children who present with some or all of the diagnostic criteria, if these children are exposed to environmental factors that might put them at risk (substandard housing, old paint, proximity to a highway which led to deposition of lead in the topsoil from automobile exhaust years ago). Behavior in the structured laboratory setting might not reflect the child’s typical behavior in the home or school environment. Therefore, reliance on observed behavior in a physician’s office can result in an incorrect diagnosis. Computerized attentional tasks and electroencephalographic assessments are not needed to make the diagnosis, and compared to the clinical gold standard they are subject to false-positive and false-negative errors. Nonetheless, the FDA has approved the Neuropsychiatric EEG-Based Assessment Aide (NEBA) system, which may identify an abnormal theta/beta wave ratio associated with ADHD.

Differential Diagnosis

Chronic illnesses, such as migraine headaches, absence seizures, asthma and allergies, hematologic disorders, diabetes, childhood cancer, affect up to 20% of children in the United States and can impair children’s attention and school performance, either because of the disease itself or because of the medications used to treat or control the underlying illness (medications for asthma, steroids, anticonvulsants, antihistamines) (see Table 33-3). In older children and adolescents, substance abuse (see Chapter 11) can result in declining school performance and inattentive behavior.

Sleep disorders, including those secondary to chronic upper airway obstruction from enlarged tonsils and adenoids, often result in behavioral and emotional symptoms, although such problems are not likely to be principal contributing causes of ADHD (see Chapter 19). Periodic leg movements of sleep/restless leg syndrome is associated with attentional symptoms, and inquiry regarding this should be made during the history. Behavioral and emotional disorders can cause disrupted sleep patterns as well.

Depression and anxiety disorders (see Chapters 25 and 26) can cause many of the same symptoms as ADHD (inattention, restlessness, inability to focus and concentrate on work, poor organization, forgetfulness), but can also be comorbid conditions. Obsessive-compulsive disorder can mimic ADHD, particularly when recurrent and persistent thoughts, impulses, or images are intrusive and interfere with normal daily activities. Adjustment disorders secondary to major life stresses (death of a close family member, parents’ divorce, family violence, parents’ substance abuse, a move, shared social trauma such as bombings or other attacks) or parent–child relationship disorders involving conflicts over discipline, overt child abuse and/or neglect, or overprotection can result in symptoms similar to those of ADHD.

Although ADHD is believed to result from primary impairment of attention, impulse control, and motor activity, there is a high prevalence of comorbidity with other neuropsychiatric disorders (see Table 33-3). Of children with ADHD, 15–25% have learning disabilities, 30–35% have developmental language disorders, 15–20% have

<table>
<thead>
<tr>
<th>Table 33-2</th>
<th>Differences Between U.S. and European Criteria for ADHD or HKD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DSM-5 ADHD</strong></td>
<td><strong>ICD-10 HKD</strong></td>
</tr>
<tr>
<td><strong>SYMPTOMS</strong></td>
<td><strong>SYMPTOMS</strong></td>
</tr>
<tr>
<td>Either or both of following:</td>
<td>All of following:</td>
</tr>
<tr>
<td>At least 6 of 9 inattentive symptoms</td>
<td>At least 6 of 8 inattentive symptoms</td>
</tr>
<tr>
<td>At least 6 of 9 hyperactive or impulsive symptoms</td>
<td>At least 3 of 5 hyperactive symptoms</td>
</tr>
<tr>
<td><strong>PERVASIVENESS</strong></td>
<td><strong>PERVASIVENESS</strong></td>
</tr>
<tr>
<td>Some impairment from symptoms is present in &gt;1 setting</td>
<td>Criteria are met for &gt;1 setting</td>
</tr>
</tbody>
</table>

ADHD, attention-deficit/hyperactivity disorder; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; HKD, hyperkinetic disorder; ICD-10, International Classification of Diseases, 10th edition.


<table>
<thead>
<tr>
<th>Table 33-3</th>
<th>Differential Diagnosis of Attention-Deficit/Hyperactivity Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSYCHOSOCIAL FACTORS</strong></td>
<td><strong>DIAGNOSES ASSOCIATED WITH ADHD BEHAVIORS</strong></td>
</tr>
<tr>
<td>Response to physical or sexual abuse</td>
<td>Fragile X syndrome</td>
</tr>
<tr>
<td>Response to inappropriate parenting practices</td>
<td>Fetal alcohol syndrome</td>
</tr>
<tr>
<td>Response to parental psychopathology</td>
<td>Pervasive developmental disorders</td>
</tr>
<tr>
<td>Response to acculturation</td>
<td>Obsessive-compulsive disorder</td>
</tr>
<tr>
<td>Response to inappropriate classroom setting</td>
<td>Gilles de la Tourette syndrome</td>
</tr>
<tr>
<td><strong>DIAGNOSES AND NEUROLOGIC CONDITIONS</strong></td>
<td>Attachment disorder with mixed emotions and conduct</td>
</tr>
<tr>
<td>Thyroid disorders (including general resistance to thyroid hormone)</td>
<td><strong>MEDICAL AND NEUROLOGIC CONDITIONS</strong></td>
</tr>
<tr>
<td>Heavy metal poisoning (including lead)</td>
<td><strong>SYMPTOMS</strong></td>
</tr>
<tr>
<td>Adverse effects of medications</td>
<td>At least 6 of 9 inattentive symptoms</td>
</tr>
<tr>
<td>Effects of abused substances</td>
<td>At least 6 of 8 inattentive symptoms</td>
</tr>
<tr>
<td>Sensory deficiencies (hearing and vision)</td>
<td>At least 3 of 5 hyperactive symptoms</td>
</tr>
<tr>
<td>Auditory and visual processing disorders</td>
<td>At least 1 of 4 impulsive symptoms</td>
</tr>
<tr>
<td>Neurodegenerative disorder, especially leukodystrophies</td>
<td><strong>PERVASIVENESS</strong></td>
</tr>
<tr>
<td>Posttraumatic head injury</td>
<td>Some impairment from symptoms is present in &gt;1 setting</td>
</tr>
<tr>
<td>Postencephalitic disorder</td>
<td>Criteria are met for &gt;1 setting</td>
</tr>
<tr>
<td><strong>FACTORS</strong></td>
<td><strong>PERVASIVENESS</strong></td>
</tr>
<tr>
<td><strong>NEUROLOGIC</strong></td>
<td><strong>PERVASIVENESS</strong></td>
</tr>
<tr>
<td>Effects of abused substances</td>
<td>Some impairment from symptoms is present in &gt;1 setting</td>
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</tr>
</tbody>
</table>

Note: Coexisting conditions with possible ADHD presentation include oppositional defiant disorder, anxiety disorders, conduct disorder, depressive disorders, learning disorders, and language disorders. Presence of 1 or more of the symptoms of these disorders can fall within the spectrum of normal behavior, whereas a range of these symptoms may be problematic but fall short of meeting the full criteria for the disorder.

diagnosed mood disorders, and 20-25% have coexisting anxiety disorders. Children with ADHD can also have co-occurring diagnoses of sleep disorders, memory impairment, and decreased motor skills.

**TREATMENT**

**Psychosocial Treatments**

Once the diagnosis of ADHD is established, the caregiver should discuss with the parents and child the ways ADHD can affect learning, behavior, self-esteem, social skills, and family function. The clinician should set goals for the family to improve the child’s interpersonal relationships, develop study skills, and decrease disruptive behaviors. Parent support groups with appropriate professional consultation to such groups can be very helpful.

**Behaviorally Oriented Treatments**

Treatments geared toward behavioral management often occur in the time frame of 8-12 sessions. The goal of such treatment is for the clinician to identify targeted behaviors that cause impairment in the child’s life (disruptive behavior, difficulty in completing homework, failure to obey home or school rules) and for the child to work on progressively improving the child’s skill in these areas. The clinician should guide the parents and teachers in implementing rules, consequences, and rewards to encourage desired behaviors. In short-term comparison trials, stimulants have been more effective than behavioral treatments used alone; behavioral interventions are only modestly successful at improving behavior, but they may be particularly useful for children with complex comorbidities and family stressors, when combined with medication.

**Medications**

The most widely used medications for the treatment of ADHD and the treatment of choice are the presynaptic dopaminergic agonists, commonly called psychostimulant medications, including methylphenidate (Ritalin, Concerta, Metadate, Focalin, Daytrana), amphetamine, and/or various amphetamine and dextroamphetamine preparations (Dexedrine, Adderall, Vyvanse) (Table 33-4). Longer-acting, once-daily forms of each of the major types of stimulant medications are available and facilitate compliance with treatment and coverage over a longer period of time. The clinician should prescribe a stimulant treatment, either methylphenidate or an amphetamine compound. If a full range of methylphenidate dosages is used, approximately 25% of patients have an optimal response on a low (≤0.5 mg/kg/day for methylphenidate, <0.25 mg/kg/day for amphetamines), 25% on medium (0.5-1.0 mg/kg/day for methylphenidate, 0.25-0.5 mg/kg/day for amphetamines), or high (1.0-1.5 mg/kg/day for methylphenidate, 0.5-0.75 mg/kg/day for amphetamine) daily dosage; another 25% will be unresponsive or will have side effects, making that drug particularly unpalatable for the family.

Over the first 4 wk of treatment, the physician should increase the medication dose as tolerated (keeping side effects minimal to absent) to achieve maximum benefit. If this strategy does not yield satisfactory results, or if side effects prevent further dose adjustment in the presence of persisting symptoms, the clinician should use an alternative class of stimulants that was not used previously. If a methylphenidate compound is unsuccessful, the clinician should switch to an amphetamine product. If satisfactory treatment results are not obtained with the second stimulant, clinicians may choose to prescribe atomoxetine, a noradrenergic reuptake inhibitor that is superior to placebo in the treatment of ADHD in children, adolescents, and adults and that has been approved by the FDA for this indication. Atomoxetine should be initiated at a dose of 0.3 mg/kg/day and titrated over 1-3 wk to a maximum total daily dosage of 1.2-1.8 mg/kg/day. The dose should be divided into twice-daily portions. Once-daily dosing appears to be associated with a high incidence of treatment failure. Guanfacine, originally developed as an antihypertensive agent, is also FDA approved for the treatment of ADHD, although it appears to be less successful for hyperactivity and more likely to assist with impulsivity. It can also treat motor and vocal tics, and so may be a reasonable choice in a child with a comorbid tic disorder.

The clinician should recognize that careful monitoring of medication is a necessary component of treatment in children with ADHD. When physicians prescribe medications for the treatment of ADHD, they tend to use lower-than-optimal doses. Optimal treatment usually requires somewhat higher doses than those typically used in routine practice settings. All-day preparations are also useful to maximize positive effects and minimize side effects, and regular medication follow-up visits should be offered (4 or more times per year) as opposed to the twice-yearly medication visits often used in standard community-care settings.

Medication alone is not always sufficient to treat ADHD in children, particularly in instances where children have multiple psychiatric disorders or stressed home environments. When children do not respond to medication, it may be appropriate to refer them to a mental health specialist. Consultation with a child psychiatrist or psychologist can also be beneficial to determine the next steps for treatment, including adding other components and supports to the overall treatment program. Evidence suggests that children who receive careful medication management, accompanied by frequent treatment follow-up, all within the context of an educative, supportive relationship with the primary care provider, are likely to experience behavioral gains for up to 24 mo.

Stimulant drugs used to treat ADHD may be associated with an increased risk of adverse cardiovascular events, including sudden cardiac death, myocardial infarction, and stroke in young adults and rarely in children. In some of the reported cases, the patient had an underlying disorder, such as hypertrophic obstructive cardiomyopathy, which is made worse by sympathomimetic agents. These events are rare, but they nonetheless warrant consideration before initiating treatment and during monitoring of treatment with stimulant medications. Children with a positive or personal family history of cardiomyopathy, or arrhythmias, or syncope require an electrocardiogram and possible cardiology consultation before a stimulant is prescribed (Fig. 33-1).

**PROGNOSIS**

A childhood diagnosis of ADHD often leads to persistent ADHD throughout the life span. From 60-80% of children with ADHD continue to experience symptoms in adolescence, and up to 60% of adolescents exhibit ADHD symptoms into adulthood. In children with ADHD, a reduction in hyperactive behavior often occurs with age. Other symptoms associated with ADHD can become more prominent with age, such as inattention, impulsivity, and disorganization, and...
these exact a heavy toll on young adult functioning. A variety of risk factors can affect children with untreated ADHD as they become adults. These risk factors include engaging in risk-taking behaviors (sexual activity, delinquent behaviors, substance use), educational underachievement or employment difficulties, and relationship difficulties. With proper treatment, the risks associated with the disorder can be significantly reduced. It appears that consistent treatment with medication and adjuvant therapies can lower the risk of adverse outcomes, such as substance abuse.

**PREVENTION**

Parent training can lead to significant improvements in preschool children with ADHD symptoms, and parent training for preschool youth with ADHD can reduce oppositional behavior. To the extent that parents, teachers, physicians, and policymakers support efforts for earlier detection, diagnosis, and treatment, prevention of long-term adverse effects of ADHD on affected children’s lives should be reconsidered within the lens of prevention. Given the effective treatments for ADHD now available, and the well-documented evidence about the long-term effects of untreated or ineffectively treated ADHD on children and youth, prevention of these consequences should be within the grasp of physicians and the children and families with ADHD for whom we are responsible.

Bibliography is available at Expert Consult.
Bibliography


FDA Drug Safety Communication: FDA warns of rare risk of long-lasting erections in males taking methylphenidate ADHD medications and has approved label changes. Available at: http://www.fda.gov/drugs/drugsafety/ucm375796.htm.


Dyslexia is defined in this chapter as an unexpected difficulty in reading, that is, unexpected in relation to intelligence, chronological age/grade level, education, or professional status. In typical readers, development of reading and IQ are dynamically linked over time, but in dyslexic readers there is a developmental uncoupling between reading and IQ (Fig. 34-1). These findings provide an explanation for the “unexpected” nature of dyslexia and provide the long sought empirical evidence for the seeming paradox between cognition and reading in individuals with developmental dyslexia.

ETIOLOGY
Dyslexia is both familial and heritable. Dyslexia is observed in 50% of children who have a parent with dyslexia; 50% of the siblings of dyslexic persons; and 50% of the parents of dyslexics. Dyslexia reflects a multifactorial model of the interaction between genetic and environmental factors. Multiple genes can influence the disorder, with each gene individually contributing a small amount of variance and with a single etiologic factor insufficient to cause or explain dyslexia. The neural systems are the final common pathway for multiple influences, and it is unlikely that a single gene or even several genes cause or explain dyslexia.

EPIDEMIOLOGY
Dyslexia is the most common and most comprehensively studied of the learning disabilities, affecting 80% of children identified as learning disabled. Dyslexia may be the most common neurobehavioral disorder affecting children, with prevalence rates ranging from 5-10% in clinic- and school-identified samples to 17.5% in unselected population-based samples in the United States and other countries. Dyslexia fits a dimensional model in which reading ability and disability occur along a continuum, with dyslexia representing the lower tail of a normal distribution of reading ability. Although more boys than girls are identified by schools as dyslexic, in studies based on survey samples in which all children are assessed, there are no significant gender differences in dyslexia.

PATHOGENESIS
Evidence from a number of lines of investigation indicates that dyslexia reflects deficits within the language system, and more specifically, within the phonologic component of the language system engaged in processing the sounds of speech. Dyslexic individuals have difficulty developing an awareness that spoken words can be segmented into smaller elemental units of sound (phonemes), an essential ability given that reading requires that the reader map or link printed symbols to sound. Increasing evidence indicates that disruption of attentional mechanisms may also play an important role in reading difficulties.

Functional brain imaging in both children with dyslexia and adult dyslexic readers demonstrates an inefficient functioning of left hemisphere posterior brain systems, a pattern referred to as the neural signature of dyslexia (Fig. 34-2). Although functional MRI consistently demonstrates differences between groups of dyslexic compared to typical readers, brain imaging is not able to differentiate an individual case of dyslexic reader from a typical reader and so brain imaging is not useful in diagnosing dyslexia.

CLINICAL MANIFESTATIONS
Reflecting the underlying phonologic weakness, children and adults with dyslexia manifest problems in both spoken and written language. Spoken language difficulties are typically manifest by mispronunciations, lack of glibness, speech that lacks fluency with many pauses or hesitations and “ums,” word-finding difficulties with the need for time to summon an oral response and the inability to come up with a verbal response quickly when questioned; these reflect sound-based, and not semantic or knowledge-based difficulties.

Struggles in decoding and word identification can vary according to age and developmental level. The cardinal signs of dyslexia observed in school-age children and adults are a labored, effortful approach to reading involving decoding, word recognition, and text reading. Listening comprehension is typically robust. Older children improve reading accuracy over time, albeit without commensurate gains in reading fluency; they remain slow readers. Difficulties in spelling typically reflect the phonologically based difficulties observed in oral reading. Handwriting is often affected as well.

History often reveals early subtle language difficulties in dyslexic children. During the preschool and kindergarten years, at-risk children display difficulties playing rhyming games and learning the names for letters and numbers. Kindergarten assessments of these language skills can help identify children at risk for dyslexia. Although a dyslexic child enjoys and benefits from being read to, the child might avoid reading aloud to the parent or reading independently.

Figure 34-2 A neural signature for dyslexia. The left side of the figure shows a schematic of left hemisphere brain systems in typical (non-impaired) readers. The 3 systems for reading are an anterior system in the region of the inferior frontal gyrus (Broca’s area), serving articulation and word analysis, and 2 posterior systems, 1 in the occipitotemporal region serving word analysis, and a second in the occipitotemporal region (the word-form area) serving the rapid, automatic, fluent identification of words. In dyslexic readers (right side of figure), the 2 posterior systems are functioning inefficiently and appear underactivated. This pattern of underactivation in left posterior reading systems is referred to as the neural signature for dyslexia. (Adapted from Shaywitz S. Overcoming dyslexia: a new and complete science-based program for reading problems at any level. New York, 2003; Alfred A. Knopf. Copyright 2003 by S. Shaywitz. Adapted with permission.)
Dyslexia may co-occur with attention-deficit/hyperactivity disorder (see Chapter 33); this comorbidity has been documented in both referred samples (40% comorbidity) and nonreferred samples (15% comorbidity).

**DIAGNOSIS**

Dyslexia is a clinical diagnosis, and history is especially critical. The clinician seeks to determine through history, observation, and psychometric assessment, if there are unexpected difficulties in reading (based on the person’s intelligence, chronological/grade, level of education or professional status) and associated linguistic problems at the level of phonologic processing. There is no single test score that is pathognomonic of dyslexia. The diagnosis of dyslexia should reflect a thoughtful synthesis of all clinical data available.

Dyslexia is distinguished from other disorders that can prominently feature reading difficulties by the unique, circumscribed nature of the phonologic deficit, one that does not intrude into other linguistic or cognitive domains. Family history, teacher and classroom observation, and tests of language (particularly phonology), reading including fluency, and spelling represent a core assessment for the diagnosis of dyslexia in children; additional tests of intellectual ability, attention, memory, general language skills, and mathematics may be administered as part of a more comprehensive evaluation of cognitive, linguistic, and academic function. Once a diagnosis has been made, dyslexia is a permanent diagnosis and need not be reconfirmed by new assessments.

For informal screening, in addition to a careful history, the primary care physician in an office setting can listen to the child read aloud from the child’s own grade-level reader. Keeping a set of graded readers available in the office serves the same purpose and eliminates the need for the child to bring in schoolbooks. Oral reading is a sensitive measure of reading accuracy and fluency. The most consistent and telling sign of a reading disability in an accomplished young adult is slow and laborious reading and writing. In attempting to read aloud, most children and adults with dyslexia display an effortful approach to decoding and recognizing single words, an approach in children characterized by hesitations, mispronunciations, and repeated attempts to sound out unfamiliar words. In contrast to the difficulties they experience in decoding single words, persons with dyslexia typically possess the vocabulary, syntax, and other higher-level abilities involved in comprehension.

The failure either to recognize or to measure the lack of fluency in reading is perhaps the most common error in the diagnosis of dyslexia in older children and accomplished young adults. Simple word identification tasks will not detect dyslexia in a person who is accomplished enough to be in honors high school classes or to graduate from college or obtain a graduate degree. Tests relying on the accuracy of word identification alone are inappropriate to use to diagnose dyslexia because they show little to nothing of the struggle to read. Because they assess reading accuracy but not automatically (speed), the kinds of reading tests commonly used for school-age children might provide misleading data on bright adolescents and young adults. The most critical tests are those that are timed; they are the most sensitive in detecting dyslexia in a bright adult. There are few standardized tests for young adult readers that are administered under timed and untimed conditions; the Nelson-Denny Reading Test is an exception. The helpful Test of Word Reading Efficiency (TOWRE) examines simple word reading under timed conditions. Any scores obtained on testing must be considered relative to peers with the same degree of education or professional training.

**MANAGEMENT**

The management of dyslexia demands a life-span perspective. Early on, the focus is on remediation of the reading problem. Application of knowledge of the importance of early language, including vocabulary and phonologic skills, leads to significant improvements in children’s reading accuracy, even in predisposed children. As a child matures and enters the more time-demanding setting of secondary school, the emphasis shifts to the important role of providing accommodations. Based on the work of the National Reading Panel, evidence-based reading intervention methods and programs are identified. Effective intervention programs provide systematic instruction in 5 key areas: phonemic awareness, phonics, fluency, vocabulary, and comprehension strategies. These programs also provide ample opportunities for writing, reading, and discussing literature.

Taking each component of the reading process in turn, effective interventions improve **phonemic awareness**: the ability to focus on and manipulate phonemes (speech sounds) in spoken syllables and words. The elements found to be most effective in enhancing phonemic awareness, reading, and spelling skills include teaching children to manipulate phonemes with letters; focusing the instruction on 1 or 2 types of phoneme manipulations rather than multiple types; and teaching children in small groups. Providing instruction in phonemic awareness is necessary but not sufficient to teach children to read. Effective intervention programs include teaching **phonics**, or making sure that the beginning reader understands how letters are linked to sounds (phonemes) to form letter-sound correspondences and spelling patterns. The instruction should be explicit and systematic; phonics instruction enhances children’s success in learning to read, and systematic phonics instruction is more effective than instruction that teaches little or no phonics or teaches phonics casually or haphazardly.

**Fluency** is of critical importance because it allows the automatic, rapid recognition of words and while it is generally recognized that fluency is an important component of skilled reading, it has proven difficult to teach. Interventions for **vocabulary development and reading comprehension** are not as well established. The most effective methods to teach reading comprehension involve teaching **vocabulary** and **strategies** that encourage active interaction between the reader and the text. Emerging science indicates that it is not only teacher content knowledge but the teacher’s skill in engaging the student and focusing the student’s attention on the reading task at hand that is required for effective instruction.

For those in high school, college, and graduate school, provision of accommodations most often represents a highly effective approach to dyslexia. Imaging studies now provide neurobiologic evidence for the need for extra time for dyslexic students; accordingly, college students with a childhood history of dyslexia require extra time in reading and writing assignments as well as examinations. Many adolescent and adult students have been able to improve their reading accuracy but without commensurate gains in reading speed. The accommodation of extra time reconciles the individual’s often high cognitive ability and slow reading so that the exam is a measure of that person’s ability rather than his disability. Another important accommodation is teaching the dyslexic student to listen to texts. Programs such as Kurzweil, WYNN, Learning Ally, and Bookshare are available, as are programs such as Dragon Dictate that provide voice-to-text conversion. Other helpful accommodations include the use of laptop computers with spelling checkers, access to lecture notes, tutorial services, and a separate quiet room for taking tests. In addition, the impact of the primary phonologic weakness mandates special consideration during oral examinations so that students are not graded on their lack of glibness or speech hesitancies but on their content knowledge. Unfortunately, often speech hesitancies or difficulties in word retrieval are wrongly confused with insecure content knowledge.

**PROGNOSIS**

Application of evidence-based methods to young children (kindergarten to grade 3), when provided with sufficient intensity and duration, can result in improvements in reading accuracy and, to a much lesser extent, fluency. In older children and adults, interventions result in improved accuracy, but not an appreciable improvement in fluency. Accommodations are critical in allowing the dyslexic child to demonstrate his or her knowledge. Parents should be informed that with proper support, dyslexic children can succeed in a range of future occupations that might seem out of the reach of dyslexic children including medicine, law, journalism, and writing.

Bibliography is available at Expert Consult.
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National Reading Panel: Teaching children to read: an evidence based assessment of the scientific research literature on reading and its implications for reading instruction (NIH pub. no. 00-4754), Bethesda, MD, 2000, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Child Health and Human Development.
Most children learn to communicate in their native language without specific instruction or intervention other than exposure to a language-rich environment. Normal development of speech and language is predicated on the infant's ability to hear, see, comprehend, remember, and socially interact with others. The infant must also possess sufficient motor skills to imitate oral motor movements.

**NORMAL LANGUAGE DEVELOPMENT**

Language can be subdivided into several essential components. Communication consists of a wide range of behaviors and skills. At the level of basic verbal ability, phonology refers to the correct use of speech sounds to form words, semantics refers to the correct use of words, and syntax refers to the appropriate use of grammar to make sentences. At a more abstract level, verbal skills include the ability to link thoughts together in a coherent fashion and to maintain a topic of conversation.

Pragmatic abilities include verbal and nonverbal skills that facilitate the exchange of ideas, including the appropriate choice of language for the situation and circumstance and the appropriate use of body language (i.e., posture, eye contact, gestures). Social pragmatic and behavioral skills also play an important role in effective interactions with communication partners (i.e., engaging, responding, and maintaining reciprocal exchanges).

It is customary to divide language skills into receptive (hearing and understanding) and expressive (talking) abilities. Language development usually follows a fairly predictable pattern and parallels general intellectual development (Table 35-1).

**Receptive Language Development**

The peripheral auditory system is mature by 26 wk gestation and the fetus responds to and discriminates speech sounds. Anatomical asymmetry in the planum temporale, the structural brain region specialized for language processing, is present by 31 wk gestation. At birth, the full-term newborn appears to have functionally organized neural networks that are sensitive to different properties of language input. The normal newborn demonstrates preferential response to human voices over inanimate sound, and recognizes the mother's voice, reacting stronger to it than to a stranger's voice. Even more remarkable is the ability of the newborn to discriminate sentences in their native (mother's) language from sentences in a foreign language. In research settings, infants of monolingual mothers showed a preference only for that language, while infants of bilingual mothers showed a preference for both exposed languages over any other language.

Between 4 and 6 mo, infants visually search for the source of sounds, again showing a preference for the human voice over other environmental sounds. By 5 mo, infants can passively follow the adult's line of visual regard, resulting in a joint reference to the same objects and events in the environment. The ability to share the same experience is critical to the development of further language, social, and cognitive skills as the infant maps specific meanings onto his or her experiences. By 8 mo, the infant can actively show, give, and point to objects. Comprehension of words often becomes apparent by 9 mo, when the infant selectively responds to his or her name and appears to comprehend the word “no.” Social games, such as “peek-a-boo,” “so big,” and waving “bye-bye” can be elicited by simply mentioning the words. At 12 mo, many children can follow a simple, one-step request without a gesture (e.g., “Give it to me!”).

Between 1 and 2 yr, comprehension of language accelerates rapidly. Toddlers can point to body parts on command, identify pictures in books when named, and respond to simple questions (e.g., “Where’s your shoe?”). The 2 yr old is able to follow a 2-step command, employing unrelated tasks (e.g., “Take off your shoes, then go sit at the table”), and can point to objects described by their use (e.g., “Give me the one we drink from”). By 3 yr, children typically understand simple “wh-” question forms (e.g., who, what, where, why). By 4 yr, most children can follow adult conversation. They can listen to a short story and answer simple questions about it. Five yr olds typically have a receptive vocabulary of more than 2000 words and can follow 3- and 4-step commands.

**Expressive Language Development**

Cooing noises are established by 4-6 wk of age. Over the first 3 mo of life, parents may distinguish their infant's different vocal sounds for pleasure, pain, fussing, tiredness, etc. Many 3 mo old infants vocalize in a reciprocal fashion with an adult to maintain a social interaction (“vocal tennis”). By 4 mo, infants begin to make bilabial (“raspberry”) sounds, and by 5 mo, monosyllables and laughings are noticeable. Between 6 and 8 mo, polysyllabic babbling (“lalala” or “mamama”) is heard and the infant might begin to communicate with gestures. Between 8 and 10 mo, babbling makes a phonologic shift toward the particular sound patterns of the child's native language (i.e., they produce more native sounds than nonnative sounds). At 9-10 mo, babbling becomes truncated into specific words (e.g., “mama,” or “dada”) for their parents.

Over the next several months, infants learn 1 or 2 words for common objects and begin to imitate words presented by an adult. These words might appear to come and go from the child's repertoire until a stable group of 10 or more words is established. The rate of acquisition of new words is approximately 1 new word per wk at 12 mo, but it accelerates to approximately 1 new word per day by 2 yr. The first words to appear are used primarily to label objects (nouns) or to ask for objects and people (requests). By 18-20 mo, toddlers should use a minimum of 20 words and produce jargon (strings of word-like sounds) with language-like inflection patterns (rising and falling speech patterns). This jargon usually contains some embedded true words. Spontaneous 2-word phrases (pivotal speech), consisting of the flexible juxtaposition of words with clear intention (e.g., “Want juice!” or “Me down!”), is characteristic of 2 yr olds and reflects the emergence of grammatical ability (syntax).

Two-word, combinational phrases do not usually emerge until the child has acquired 50-100 words in their lexicon. Thereafter, the acquisition of new words accelerates rapidly. As knowledge of grammar increases, there is a proportional increase in verbs, adjectives, and other words that serve to define the relation between objects and people (predicates). By 3 yr, sentence length increases and the child uses pronouns and simple present tense verb forms. These 3-5 word sentences typically have a subject and verb but lack conjunctions, articles, and complex verb forms. The Sesame Street character Cookie Monster (“Me want cookie!”) typifies the telegraphic nature of the 3 yr old's sentences. By 4-5 yr, children should be able to carry on conversations using adult-like grammatical forms and use sentences that provide details (e.g., “I like to read my books”).

**Variations of Normal**

Language milestones have been found to be largely universal across languages and cultures, with some variations depending on the complexity of the grammatical structure of individual languages. In Italian (where verbs often occupy a prominent position at the beginning or end of sentences), 14 month-olds produce a greater proportion of verbs compared with English speaking infants. Within a given language, development usually follows a fairly predictable pattern, parallelizing general cognitive development. Although the sequences are predictable, the exact timing of achievement is not. There are marked variations among normal children in the rate of development of babbling, comprehension of words, production of single words, and use of combinational forms within the first 2-3 yr of life.
**Table 35-1 Normal Language Milestones**

<table>
<thead>
<tr>
<th>HEARING AND UNDERSTANDING</th>
<th>TALKING</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BIRTH TO 3 MONTHS</strong></td>
<td></td>
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<tr>
<td>Startles to loud sounds</td>
<td>Makes pleasure sounds (cooing, gooing)</td>
</tr>
<tr>
<td>Quiets or smiles when spoken to</td>
<td>Cries differently for different needs</td>
</tr>
<tr>
<td>Seems to recognize your voice and quiets if crying</td>
<td>Smiles when you see you</td>
</tr>
<tr>
<td>Increases or decreases sucking behavior in response to sound</td>
<td></td>
</tr>
<tr>
<td><strong>4-6 MO</strong></td>
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</tr>
<tr>
<td>Moves eyes in direction of sounds</td>
<td>Babbling sounds more speech-like, with many different sounds, including $p$, $b$, and $m$</td>
</tr>
<tr>
<td>Responds to changes in tone of your voice</td>
<td>Vocalizes excitement and displeasure</td>
</tr>
<tr>
<td>Notices toys that make sounds</td>
<td>Makes gurgling sounds when left alone and when playing with you</td>
</tr>
<tr>
<td>Pays attention to music</td>
<td></td>
</tr>
<tr>
<td><strong>7 MO-1 YEAR</strong></td>
<td></td>
</tr>
<tr>
<td>Enjoys games such as peekaboo and pat-a-cake</td>
<td>Babbling has both long and short groups of sounds, such as tata upup bibibibi.</td>
</tr>
<tr>
<td>Turns and looks in direction of sounds</td>
<td>Uses speech or noncrying sounds to get and keep attention</td>
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<tr>
<td>Listens when spoken to</td>
<td>Imitates different speech sounds</td>
</tr>
<tr>
<td>Recognizes words for common items, such as cup, shoe, and juice</td>
<td>Has 1 or 2 words (bye-bye, Dada, Mama), although they might not be clear</td>
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<tr>
<td>Begins to respond to requests (Come here. Want more?)</td>
<td></td>
</tr>
<tr>
<td><strong>1-2 YR</strong></td>
<td></td>
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<tr>
<td>Points to a few body parts when asked</td>
<td>Says more words every month</td>
</tr>
<tr>
<td>Follows simple commands and understands simple questions (Roll the ball. Kiss the baby. Where’s your shoe?)</td>
<td>Uses some 1-2 word questions (Where kitty? Go bye-bye? What’s that?)</td>
</tr>
<tr>
<td>Listens to simple stories, songs, and rhymes</td>
<td>Puts 2 words together (more cookie, no juice, mommy book)</td>
</tr>
<tr>
<td>Points to pictures in a book when named</td>
<td>Uses many different consonant sounds at the beginning of words</td>
</tr>
<tr>
<td><strong>2-3 YR</strong></td>
<td></td>
</tr>
<tr>
<td>Understands differences in meaning (e.g., go–stop, in–on, big–little, up–down)</td>
<td>Has a word for almost everything</td>
</tr>
<tr>
<td>Follows 2-step requests (Get the book and put it on the table.)</td>
<td>Uses 2-3 word “sentences” to talk about and ask for things</td>
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<tr>
<td></td>
<td>Speech is understood by familiar listeners most of the time</td>
</tr>
<tr>
<td></td>
<td>Often asks for or directs attention to objects by naming them</td>
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<tr>
<td><strong>3-4 YR</strong></td>
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<tr>
<td>Hears you when you call from another room</td>
<td>Talks about activities at school or at friends’ homes</td>
</tr>
<tr>
<td>Hears television or radio at the same loudness level as other family members</td>
<td>Usually understood by people outside the family</td>
</tr>
<tr>
<td>Understands simple who, what, where, why questions</td>
<td>Uses a lot of sentences that have 2-8 words</td>
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<tr>
<td></td>
<td>Usually talks easily without repeating syllables or words</td>
</tr>
<tr>
<td><strong>4-5 YR</strong></td>
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<tr>
<td>Pays attention to a short story and answers simple questions about it</td>
<td>Voice sounds as clear as other children’s</td>
</tr>
<tr>
<td>Hears and understands most of what is said at home and in school</td>
<td>Uses sentences that include details (I like to read my books.)</td>
</tr>
<tr>
<td></td>
<td>Tells stories that stick to a topic</td>
</tr>
<tr>
<td></td>
<td>Communicates easily with other children and adults</td>
</tr>
<tr>
<td></td>
<td>Says most sounds correctly except a few, such as $l$, $s$, $r$, $v$, $z$, $ch$, $sh$, and $th$</td>
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<tr>
<td></td>
<td>Uses the same grammar as the rest of the family</td>
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Two basic patterns of language learning have been identified: “analytic” and “holistic.” The analytic pattern is the most common and reflects the mastery of increasingly larger units of language form. As reflected in the previous discussion of milestones, the child’s analytic skills proceed from simple to more complex and lengthy forms. Children who follow a holistic or gestalt learning pattern might start by using relatively large chunks of speech in familiar contexts. They might memorize familiar phrases or dialogs from movies or stories and repeat them in an over-generalized fashion. Their sentences often have a formulaic pattern, reflecting inadequate mastery of the use of grammar to flexibly and spontaneously combine words appropriately in the child’s own unique utterance. Over time, these children gradually break down the meanings of phrases and sentences into their component parts, and they learn to analyze the linguistic units of these memorized forms. As this occurs, more original speech productions emerge and the child is able to assemble thoughts in a more flexible manner. Both analytic and holistic learning processes are necessary for normal language development to occur.

**LANGUAGE AND COMMUNICATION DISORDERS**

**Epidemiology**

Disorders of speech and language are very common in preschool-age children. Nearly 20% of 2 yr olds are thought to have delayed onset of speech. By age 5 yr, approximately 6% of children are identified as having a speech impairment, 5% as having both speech and language impairment, and 8% as having language impairment. Boys are nearly twice as likely to have an identified speech or language impairment as girls.

**Etiology**

Normal language ability is a complex function that is widely distributed across the brain through interconnected neural networks that are synchronized for specific activities. Although there are clinical similarities between acquired aphasia in adults and childhood language disorders, unilateral, focal lesions acquired in early life do not seem to have the same effects in children as in adults. Risk factors for neurologic injury are absent in the vast majority of children with language impairment.

Genetic factors appear to play a major role in influencing how children learn to talk. Language disorders cluster in families. A careful family history may identify current or past speech or language problems in up to 30% of 1st-degree relatives of proband children. Although children who are exposed to parents with language difficulty might be expected to experience poor language stimulation and inappropriate language modeling, studies of twins have shown the concordance rate for low language test score and/or a history of speech therapy to be approximately 50% in dizygotic pairs, rising to over 90% in
monozygotic pairs. A number of potential gene loci have been identified, but no consistent genetic markers have been established.

The most plausible genetic mechanism involves a disruption in the timing of early prenatal neurodevelopmental events affecting migration of nerve cells from the germinal matrix to the cerebral cortex. Chromosomal lesions and point mutations of the FOXP2 gene and polymorphisms of the CNTNAP2 gene are associated with an uncommon but distinct speech and language disorder characterized by difficulties in learning and producing oral movement sequences (childhood apraxia of speech). Affected children have a spectrum of impairment in expressive and receptive language as well as problems understanding grammar.

**Pathogenesis**

Language disorders are associated with a fundamental deficit in the brain's capacity to process complex information rapidly. Simultaneous evaluation of words (semantics), sentences (syntax), prosody (tone of voice), and social cues can overtax the child's ability to comprehend and respond appropriately in a verbal setting. Limitations in the amount of information that can be stored in verbal working memory can further limit the rate at which language information is processed. Electrophysiologic studies show abnormal latency in the early phase of auditory processing in children with language disorders. Neuroimaging studies identify an array of anatomic abnormalities in regions of the brain that are central to language processing. MRI scans in children with **specific language impairment (SLI)** may reveal white matter lesions, white matter volume loss, ventricular enlargement, focal gray matter heterotopia within the right and left perisylvian white matter, abnormal morphology of the inferior frontal gyrus, atypical patterns of asymmetry of language cortex, or increased thickness of the corpus callosum in a minority of affected children. Postmortem studies of children with language disorders found evidence of atypical symmetry in the plana temporale and cortical dysplasia in the region of the Sylvian fissure. A high incidence of paroxysmal electroencephalogram (EEG) anomalies during sleep has been identified in children with SLI. Although these findings might represent a mild variant of the Landau-Kleffner syndrome (acquired verbal auditory agnosia), they likely represent an epiphenomenon in which paroxysmal activity is related to architectural dysplasia. In support of a genetic mechanism affecting cerebral development, a high rate of atypical perisylvian asymmetries has also been documented in the parents of children with SLI.

**Clinical Manifestations**

Primary disorders of speech and language development are often found in the absence of more generalized cognitive or motor dysfunction. Disorders of communication are the most common comorbid condition in persons with generalized cognitive disorders (intellectual disability or autism), structural anomalies of the organs of speech (velopharyngeal insufficiency from cleft palate), and neuromotor conditions affecting oral motor coordination (dysarthria from cerebral palsy or other neuromuscular disorders).

**Classification**

Each professional discipline has adopted a somewhat different classification system, based on cluster patterns of symptoms. The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) organized communication disorders into: (1) language disorder (which combines expressive and mixed receptive-expressive language disorders), speech sound disorder (phonologic disorder), and childhood-onset fluency disorder (stuttering); and (2) social (pragmatic) communication disorder, which is persistent difficulties in the social uses of verbal and nonverbal communication (Table 35-2). In clinical practice, childhood speech and language disorders occur as a number of distinct entities.

**Specific Language Impairment**

Also referred to as developmental dysphasia, or developmental language disorder, SLI is characterized by a significant discrepancy between the child's overall cognitive level (typically nonverbal measures of intelligence) and functional language level. These children also follow an atypical pattern of language acquisition and use. Closer examination of the child's skills might reveal deficits in understanding and use of word meaning (semantics) and grammar (syntax). Often, children with SLI are delayed in starting to talk. Most significantly, they usually have difficulty understanding spoken language. The problem may stem from insufficient understanding of single words or from the inability to deconstruct and analyze the meaning of sentences. Many affected children show a holistic pattern of language development, repeating memorized phrases or dialog from movies or stories (echo-lalia). In contrast to their difficulty with spoken language, children with SLI appear to learn visually and demonstrate their ability on nonverbal tests of intelligence.

After children with SLI become fluent talkers, they are generally less proficient at producing oral narratives compared with their peers. Their stories tend to be shorter and include fewer propositions, main story ideas, or story grammar elements. Older children include fewer mental state descriptions (e.g., references to what their characters think and how they feel). Their narratives contain fewer cohesive devices and the story line may be difficult to follow.

Although they have difficulty interacting with peers who are more verbally adept, many children with SLI play appropriately with younger or older children. Despite their communication impairment, they engage in pretend play, show imagination, share emotions (affective reciprocity), and demonstrate joint referencing behaviors appropriate to their age. Of note is the high incidence of fine motor coordination difficulty found in these children. A combination of increased joint mobility and mild muscular hypotonia often results in motor clumsiness.

Many children with SLI show difficulties with social interaction, particularly with same-age peers. Social interaction is mediated by oral communication, and a child deficient in communication is at a distinct disadvantage in the social arena. Children with SLI tend to be more dependent on older children or adults, who can adapt their communication to match the child's level of function. Generally, social interaction skills are more closely correlated with language level than with nonverbal cognitive level. Using this as a guide, one usually sees a developmental progression of increasingly more sophisticated social interaction as the child's language abilities improve. In this context, social ineptitude is not necessarily a sign of asocial distancing (e.g., autism) but rather a delay in the ability to negotiate social interactions.

**Higher-Level Language Disorder**

As children mature, the ability to communicate effectively with others depends on mastery of a range of skills that go beyond basic understanding of words and rules of grammar. Higher-level language skills include the development of advanced vocabulary, the understanding of word relationships, reasoning skills (including drawing correct inferences and conclusions), the ability to understand things from another person's perspective, and the ability to paraphrase and rephrase with ease. In addition, higher-order language abilities include pragmatic skills that serve as the foundation for social interactions. These skills include knowledge and understanding of one's conversational partner, knowledge of the social context in which the conversation is taking place, and general knowledge of the world. Social and linguistic aspects of communication are often difficult to separate, and persons who have trouble interpreting these relatively abstract aspects of communication typically experience difficulty forming and maintaining relationships. DSM-5 Identified Social (Pragmatic) Communication Disorder (SPCD) as a category of communication disorder (Table 35-2). Symptoms of pragmatic difficulty include extreme literalness and inappropriate verbal and social interactions. Proper use and understanding of humor, slang, and sarcasm depend on correct interpretation of the meaning and the context of language and the ability to draw proper inferences. Failure to provide a sufficient referential base to one's conversational partner—to take the perspective of another person—results in the appearance of talking or behaving randomly or incoherently. SPCD often occurs in the context of SLI and autism spectrum disorder (ASD) and it has been recognized as a symptom of a wide range of disorders, including right-hemisphere damage to the brain's capacity to process complex information rapidly.
Part IV  Learning Disorders

Table 35-2  DSM-5 Diagnostic Criteria for Communication Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Criteria</th>
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</table>
| Language Disorder             | A. Persistent difficulties in the acquisition and use of language across modalities (i.e., spoken, written, sign language, or other) due to deficits in comprehension or production that include the following:  
  1. Reduced vocabulary (word knowledge and use)  
  2. Limited sentence structure (ability to put words and word endings together to form sentences based on the rules of grammar and morphology).  
  3. Impairments in discourse (ability to use vocabulary and connect sentences to explain or describe a topic or series of events or have a conversation).  
  B. Language abilities are substantially and quantifiably below those expected for age, resulting in functional limitations in effective communication, social participation, academic achievement, or occupational performance, individually or in any combination.  
  C. Onset of symptoms is in the early developmental period.  
  D. The difficulties are not attributable to hearing or other sensory impairment, motor dysfunction, or another medical or neurological condition and are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. |
| Speech Sound Disorder         | A. Persistent difficulty with speech sound production that interferes with speech intelligibility or prevents verbal communication of messages.  
  B. The disturbance causes limitations in effective communication that interfere with social participation, academic achievement, or occupational performance, individually or in any combination.  
  C. Onset of symptoms is in the early developmental period.  
  D. The difficulties are not attributable to congenital or acquired conditions, such as cerebral palsy, cleft palate, deafness or hearing loss, traumatic brain injury, or other medical or neurological conditions. |
| Social (Pragmatic) Communication Disorder | A. Persistent difficulties in the social use of verbal and nonverbal communication as manifested by all of the following:  
  1. Deficits in using communication for social purposes, such as greeting and sharing information, in a manner that is appropriate for the social context.  
  2. Impairment of the ability to change communication to match context or the needs of the listener, such as speaking differently in a classroom than on a playground, talking differently to a child than to an adult, and avoiding use of overly formal language.  
  3. Difficulties following rules for conversation and storytelling, such as taking turns in conversation, rephrasing when misunderstood, and knowing how to use verbal and nonverbal signals to regulate interaction.  
  4. Difficulties understanding what is not explicitly stated (e.g., making inferences) and nonliteral or ambiguous meanings of language (e.g., idioms, humor, metaphors, multiple meanings that depend on the context for interpretation).  
  B. The deficits result in functional limitations in effective communication, social participation, social relationships, academic achievement, or occupational performance, individually or in combination.  
  C. The onset of the symptoms is in the early developmental period (but deficits may not become fully manifest until social communication demands exceed limited capacities).  
  D. The symptoms are not attributable to another medical or neurological condition or to low abilities in the domains of word structure and grammar, and are not better explained by autism spectrum disorder, intellectual disability (intellectual developmental disorder), global developmental delay, or another mental disorder. |


Brain, Williams syndrome, and nonverbal learning disabilities. SPCD can also occur independently of other disorders. In school settings, children with SPCD may be socially ostracized and/or bullied.

**Intellectual Disability**
Most children with a mild degree of intellectual disability learn to talk at a slower-than-normal rate; they follow a normal sequence of language acquisition and eventually master basic communication skills. Difficulties may be encountered with higher-level language concepts and use. Persons with moderate to severe degrees of intellectual disability can have great difficulty in acquiring basic communication skills. About half of persons with an IQ of ≤50 are able to communicate using single words or simple phrases; the rest are typically nonverbal.

**Autism and Pervasive Developmental Disorders**
A disordered pattern of language development is one of the core features of autism and other pervasive developmental disorders (see Chapter 28). The language profile of children with autism is often indistinguishable from that in children with SLIs. The key points of distinction between these conditions are the lack of reciprocal social relationships that characterizes children with autism, limitation in the ability to develop functional, symbolic, or pretend play, and an obsessive need for sameness and resistance to change. Approximately 75-80% of children with autism are also intellectually disabled, and this can limit their ability to develop functional communication skills.

Language abilities can range from absent to grammatically intact, but with limited pragmatic features and/or odd prosody patterns. Some autistic persons have highly specialized, but isolated, “savant” skills, such as calendar calculations and hyperlexia (the precocious ability to recognize written words beyond expectation based on general intellectual ability). Regression in language and social skills (autistic regression) occurs in approximately one-third of children with autism, usually before 2 yr of age. No explanation for this phenomenon has been identified. Once the regression has “stabilized,” recovery of function does not usually occur (Fig. 35-1).

**Asperger Syndrome**
(See Chapter 28.2.)
Although sharing many characteristics of autism (deficits in social relatedness and restricted range of interests), individuals with Asperger syndrome typically show normal early language development (syntax and semantics). As they mature, higher-order social and language pragmatic impairments become prominent features of this disorder. Affected children have an unusually circumscribed range of interests, which are all-absorbing and interfere with learning of other skills and with social adaptation. These children may engage in long-winded, verbose monologues about their topics of special interest, with little regard to the reaction of others. Their inflection pattern (prosody) may be inappropriate to the content of their conversation, and they might not adjust their rate of speech or vocal volume to the setting.
Consonants may be deleted and sounds transposed. As they try to talk spontaneously, or imitate other’s speech, children with childhood apraxia of speech may display oral groping or struggling behaviors. Children with childhood apraxia of speech frequently have a history of early feeding difficulty, limited sound production as infants, and delayed onset of spoken words. They may point, grunt, or develop an elaborate gestural communication system in an attempt to overcome their verbal difficulty. Apraxia may be limited to oral-motor function, or it may be a more generalized problem affecting fine and/or gross motor coordination.

**Phonologic Disorder**

Children with phonologic speech disorder are often unintelligible, even to their parents. Articulation errors are not the result of neuromotor impairment but seem to reflect an inability to correctly process the words they hear. As a result, they lack understanding of how to fit sounds together properly to create words. In contrast to children with childhood apraxia of speech, those with phonologic disorder are fluent—although unintelligible—and produce a consistent, highly predictable pattern of articulation errors. Children with phonologic speech disorder are at high risk for later reading and learning disability.

**Hearing Impairment**

Hearing loss can be a major cause of delayed or disordered language development (see Chapter 637). Approximately 16-30 per 1,000 children have mild to severe hearing loss, significant enough to affect educational progress. In addition to these “hard of hearing” children, approximately another 1 per 1,000 are deaf (profound bilateral hearing loss). Hearing loss can be present at birth or acquired postnatally. Newborn screening programs can identify many forms of congenital hearing loss, but children can develop progressive hearing loss or acquire deafness after birth.

The most common types of hearing loss are attributable to conductive (middle ear) or sensorineural deficit. Although it is not possible to accurately predict the impact of hearing loss on a child’s language development, the type and degree of hearing loss, the age of onset, and the duration of the auditory impairment clearly play important roles. Children with significant hearing impairment often have problems developing facility with language and often have related academic difficulties. Presumably, the language impairment is caused by lack of exposure to fluent language models starting in infancy.

Approximately 30% of hearing-impaired children have at least one other disability that affects development of speech and language (e.g., intellectual disability, cerebral palsy, craniofacial anomalies). Any child who shows developmental warning signs of a speech or language problem should have a hearing assessment by an audiologist and an examination by a geneticist as part of a comprehensive evaluation.

**Hydrocephalus**

Some children with hydrocephalus may be described as having “cocktail-party syndrome.” Although they may use sophisticated words, their comprehension of abstract concepts is limited, and their pragmatic conversational skills are weak. As a result, they speak superficially about topics and appear to be carrying on a monologue (see Chapter 591.11).

**Rare Causes of Language Impairment**

**Hyperlexia**

Hyperlexia is the precocious development of reading single words that spontaneously occurs in some young children (ages 2-5 yr) without specific instruction. It is often associated with children who have a pervasive developmental disorder (see Chapter 30) or SLI. It stands in contrast to precocious reading development in young children who do not have any other developmental disorders. Hyperlexia is a variation seen in young children with disordered language who do not have the social deficits or restricted or repetitive behaviors associated with autism. A typical manifestation is for a child with SLI to orally read single words, or match pictures with single words. Although hyperlexic children show early and well-developed word-reading skills, they...
usually have no precocious ability for comprehension of text. Rather, text comprehension is closely intertwined with oral comprehension, and children who have difficulty decoding the syntax of language are also at risk for having reading comprehension problems.

**Landau-Kleffner Syndrome (Verbal Auditory Agnosia)**

Children with Landau-Kleffner syndrome have a history of normal language development until they experience a regression in their ability to comprehend spoken language (verbal auditory agnosia). The regression may be sudden or gradual, and it usually occurs between 3 and 7 yr of age. Expressive language skills typically deteriorate, and some children may become mute. Despite their language regression, these children typically retain appropriate play patterns and the ability to interact in a socially appropriate manner. An EEG might show a distinct pattern of status epilepticus in sleep (continuous spike wave in slow-wave sleep), and up to 80% of children with this condition eventually exhibit clinical seizures. A number of treatment approaches have been reported, including antiepileptic medication, steroids, and intravenous gamma globulin, with varying results. The prognosis for return of normal language ability is uncertain, even with resolution of the EEG abnormality. Epileptic interictal discharges are more frequently found on EEGs of children with language impairments than in otherwise normally developing children, even in those without any history of language regression. However, this phenomenon is believed to represent a manifestation of an underlying disorder of brain structure or function that is distinct from the language impairment, as there has been little evidence of improvement in language function when the EEG was normalized after administration of antiepileptic medication. Unless there is a clear pattern of either seizure symptoms or regression in language ability, a routine EEG is not recommended as part of the evaluation for a child with speech and/or language impairment.

**Metabolic and Neurodegenerative Disorders**

(See also Part XI.)

Regression of language development may accompany loss of neuromotor function at the outset of a number of metabolic diseases including lysosomal storage disorders (metachromatic leukodystrophy), peroxisomal disorders (adrenal leukodystrophy), ceroid lipofuscinosis (Batten disease), and mucopolysaccharidosis (Hunter disease, Hurler disease). Recently, creatine transporter deficiency was identified as an X-linked disorder that manifests with language delay in boys and mild learning disability in female carriers.

**Screening**

Developmental surveillance at each well child visit should include specific questions about normal language developmental milestones and observations of the child’s behavior. Clinical judgment, defined as eliciting and responding to parents’ concerns, can detect the majority of children with speech and language problems. Many clinicians employ standardized developmental screening questionnaires and observation checklists designed for use in a pediatrics office (see Chapter 14).

The U.S. Preventive Services Task Force reviewed screening instruments for speech and language delays in young children that can be used in primary care settings. The Task Force focused on brief measures that require <10 min to complete. There was insufficient evidence that screening instruments are more effective than using physician’s clinical observations and parents’ concerns to identify children who require further evaluation. The Task Force noted that there is no single gold standard for screening, owing to inconsistent measures and terminology, and did not recommend the use of screening instruments. Furthermore, the Task Force determined that the use of formal measures was not time or cost efficient and deferred to pediatrician’s and parents’ concerns as indicators of potential problems. Table 35-3 offers guidelines for raising concerns and referring a child for specialized speech and language evaluation. Because of the high prevalence of speech and language disorders in the general population, referral to a speech-language pathologist for further evaluation should be made whenever there is a suspicion of delay.

**NONCAUSES OF LANGUAGE DELAY**

Twinning, birth order, “laziness,” exposure to multiple languages (bilingualism), tongue-tie, or otitis media are not adequate explanations for significant language delay. Normal twins learn to talk at the same age as normal single-born children, and birth order effects on language development have not been consistently found. The drive to communicate and the rewards for successful verbal interaction are so strong that children who let others talk for them usually can’t talk for themselves and are not “lazy.” Toddlers exposed to more than 1 language can show a mild delay in starting to talk, and they can initially mix elements (vocabulary and syntax) of the different languages they are learning (code switching). However, they learn to segregate each language by 24-30 mo and are equal to their monolingual peers by 3 yr of age. An extremely tight lingual frenulum (tongue-tie) can affect feeding and speech articulation, but does not prevent the acquisition of language abilities. Finally, prospective studies show that frequent ear infections and/or serous otitis media in early childhood does not result in persisting language disorder.

**Diagnostic Evaluation**

It is important to distinguish developmental delay (abnormal timing) from developmental disorder (abnormal patterns or sequences). A child’s language and communication skills must also be interpreted within the context of the child’s overall cognitive and physical abilities. Finally, it is important to evaluate the child’s use of language to communicate with others in the broadest sense (communicative intent). Thus, a multidisciplinary evaluation is often warranted. At a minimum this should include psychologic evaluation, neurodevelopmental pediatric assessment, and speech and language examination.

**Psychologic Evaluation**

There are 2 main goals for the psychologic evaluation of a young child with a communication disorder. Nonverbal cognitive ability must be assessed to determine if the child has an intellectually disability, and the child’s social behaviors must be assessed to determine whether

<table>
<thead>
<tr>
<th><strong>Table 35-3</strong> Speech and Language Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>REFER FOR SPEECH–LANGUAGE EVALUATION IF:</td>
</tr>
<tr>
<td><strong>AT AGE</strong></td>
</tr>
<tr>
<td>15 mo</td>
</tr>
<tr>
<td>18 mo</td>
</tr>
<tr>
<td>24 mo</td>
</tr>
<tr>
<td>30 mo</td>
</tr>
<tr>
<td>36 mo</td>
</tr>
</tbody>
</table>
Cognitive Assessment

Intellectual disability is defined as deficits in cognitive abilities and adaptive behaviors. In this context, children with intellectual disability show delayed development of communication skills; however, delayed communication does not necessarily signal intellectual disability. Therefore, a broad-based cognitive assessment is an important component to the evaluation of children with language delays, including evaluation of both verbal and nonverbal skills. If a child has intellectual disability, both verbal and nonverbal scores will be low compared to norms (≤2nd percentile). In contrast, a typical cognitive profile for a child with SLI includes a significant difference between nonverbal and verbal abilities, with nonverbal IQ being greater than verbal IQ and the nonverbal score within an average range.

Evaluation of Social Behaviors

Social interest is the key difference between children with a primary language disorder (SLI) and those with a communication disorder secondary to ASD. Children with SLI have an interest in social interaction, but they may have difficulty enacting their interest because of their limitations to communication. In contrast, autistic children show little social interest. Four key nonverbal behaviors that are often shown by children with SLI—but not autistic children (especially toddlers and preschoolers)—are joint attention, affective reciprocity, pretend play, and direct imitation.

Relationship of Language and Social Behaviors to Mental Age

Cognitive assessment provides a mental age for the child, and the child’s behavior must be evaluated in that context. Most 4 yr old children typically engage peers in interactive play, but most 2 yr olds are playful but primarily focused on interactions with adult caretakers. A 4 yr old with mild to moderate intellectual disability and a mental age of 2 yr might not play with peers yet because of cognitive limitation, not a lack of desire for social interaction.

Speech and Language Evaluation

A certified speech-language pathologist should perform a speech and language evaluation. A typical evaluation includes assessment of language, speech, and the physical mechanisms associated with speech production. Both expressive and receptive language is assessed by a combination of standardized measures and informal interactions and observations. All components of language are assessed, including syntax, semantics, pragmatics, and fluency. Speech assessment similarly uses a combination of standardized measures and informal observations. Assessment of physical structures includes oral structures and function, respiratory function, and vocal quality. In many settings, a speech-language pathologist works in conjunction with an audiologist, who can do appropriate hearing evaluation of the child. If an audiologist is not available in that setting, then a separate referral should be made. No child is too young for a speech and language or hearing evaluation. A referral for evaluation is appropriate whenever there is suspicion of language impairment.

Medical Evaluation

As in any developmental disorder, careful history and physical examination should focus on the identification of potential contributors to the child’s language and communication difficulties. A family history of delay in talking, need for speech and language therapy, or academic difficulty can suggest a genetic predisposition to language disorders. Pregnancy history might reveal risk factors for prenatal developmental anomalies, such as polyhydramnios or decreased fetal movement patterns. Small size for gestational age at birth, symptoms of neonatal encephalopathy, or early and persistent oral-motor feeding difficulty may presage speech and language difficulty. Developmental history should focus on the age at which various language skills were mastered and the sequences and patterns of milestone acquisition. Regression or loss of acquired skills should raise immediate concern.

Physical examination should include measurement of height (length), weight, and head circumference. The skin should be examined for lesions consistent with phakomatosis (e.g., tuberous sclerosis, neurofibromatosis, Sturge-Weber syndrome) and other disruptions of pigment (hypomelanosis of Ito). Anomalies of the head and neck, such as white forelock and hypertelorism (Waardenburg syndrome), ear malformations (Goldenhar syndrome), facial and cardiac anomalies (Williams syndrome, velocardiofacial syndrome), or abnormalities of the chin (Pierre-Robin anomaly), or cleft lip and/or palate, are associated with hearing and speech abnormalities. Neurologic examination might reveal muscular hypertonia or hypotonia, both of which can affect neuromuscular control of speech. Generalized muscular hypotonia, with increased range of motion of the joints, is commonly seen in children with SLI. The reason for this association is not clear but it might account for the fine and gross motor clumsiness often seen in these children. However, mild hypotonia is not a sufficient explanation for the impairments of expressive and receptive language.

No routine diagnostic studies are indicated for SLI or isolated language disorders. When language delay is a part of a generalized cognitive or physical disorder, referral for further genetic evaluation, chromosomal testing (including high resolution banding karyotype, fragile X testing, and microarray comparative genomic hybridization), neuroimaging studies, and EEG may be considered, if clinically indicated.

TREATMENT

Laws emanating from the federal Individuals with Disabilities Education Act (IDEA) require that schools provide special education services to children who have learning difficulties. This includes children with speech and language disorders. Services are provided to children from birth through 21 yr of age. States have various methods for providing services, and for young children these can include Birth-to-Three, Early Childhood, and Early Learning programs. These programs provide speech–language therapy as part of public education, in conjunction with other special education resources. Children can also receive therapy from nonprofit service agencies, hospital and rehabilitation centers, and speech pathologists in private practice.

Of concern is the fact that many children with identified speech and language deficits do not receive appropriate intervention services. Population-based surveys in both the United States and Canada have found that less than half of children identified by kindergarten entry receive speech and language interventions, even when their parents have been educated about the nature of their child’s condition. In one study, children with deficits in speech–sound production were much more likely to receive services (41%) than those who had problems with language alone (9%). These findings are troubling because poor educational outcome, especially in reading, social and behavioral adjustment, are more highly associated with language than with speech–sound disorders. Therefore, the children at greatest risk are least likely to receive intervention services. Boys were twice as likely to receive speech intervention as girls, regardless of their speech–language diagnosis. Social and demographic factors did not appear to influence whether identified children received interventions services.

Speech–language therapy includes a variety of goals. Sometimes both speech and language activities are incorporated in therapy. The speech goals focus on development of more intelligible speech. Language goals can focus on expanding vocabulary (lexicon) and understanding of the meaning of words (semantics), improving syntax by using proper forms or learning to expand single words into sentences, and social use of language (pragmatics). Therapy can include individual sessions, group sessions, and mainstream classroom integration. Individual sessions may use drill activities for older children or play activities for younger children to target specific goals. Group sessions can include several children with similar language goals to help them practice peer communication activities and to help them bridge the gap into more naturalistic communication situations. Classroom
integration might include the therapist team-teaching or consulting with the teacher to facilitate the child's use of language in common academic situations.

For children with severe language impairment, alternative methods of communication are often included in therapy. These may include use of manual sign language, use of pictures (e.g., Picture Exchange Communication System), and computerized devices for speech output. Often the ultimate goal is to achieve better spoken language. Early use of signs or pictures can help the child to establish better functional communication and help the child to understand the symbolic nature of words to facilitate the language process. There is no evidence that use of signs or pictures interferes with development of oral language if the child has the capacity to speak. Many clinicians believe that these alternative methods accelerate the learning of language. They also reduce frustration of parents and children who cannot communicate for basic needs.

Parents can consult with their child's speech-language therapist about home activities to enhance language development and extend therapy activities through appropriate language-stimulating activities and recreational reading. Parents' language activities should focus on emerging communication skills that are within the child's repertoire, rather than teaching the child new skills. The speech pathologist can guide parents on effective modeling and eliciting communication from their child.

Recreational reading focuses on expanding the child's comprehension of language. Sometimes the child's avoidance of reading is a sign that the parent is presenting material that is too complex for the child. The speech-language therapist can guide the parent in selecting an appropriate level of reading material.

PROGNOSIS
Children with isolated expressive language disorder (“late talkers”) have an excellent prognosis for both language, learning, and social–emotional adjustment.

Over time, children with SLI respond to therapeutic/educational interventions and show a trend toward improvement of communication skills. Adults with a history of childhood language disorder continue to show evidence of impaired language ability, even when surface features of the communication difficulty have improved considerably. This suggests that many persons find successful ways of adapting to their impairment. Although the majority of children improve their communication ability with time, 50–80% of preschoolers with language delay and normal nonverbal intelligence continue to experience difficulty with language and social development up to 20 yr beyond the initial diagnosis. Language disorders often interfere with the child's ability to conceptualize the increasingly complex and ambiguous worlds of social relationship and emotions. As a consequence, in later childhood and adolescence, children with persisting symptoms of SLI are about twice as likely as their typical language peers to show clinical levels of emotional problems and twice as likely to show behavioral difficulties. A Danish study found that adults with SLI were less likely to have completed formal education beyond high school and to have lower occupational and socioeconomic success than the general population. Fifty-six percent held a paid job (vs 84% of the same age general population), of which 35% were unskilled and 40% were skilled workers. Eighty percent of the adults reported having had difficulty reading while in school and most had received remedial teaching, and 50% continued to report reading difficulty as adults (compared with 5% of Danish adults). Lower non-verbal intelligence and comorbid psychiatric and/or neurologic disorders independently contributed to a worse prognosis. These results were consistent with previous reports of adult outcomes of children with SLI from Canada and the United Kingdom.

Academic Disorders
Early language difficulty is strongly related to later reading disorder. Approximately 50% of children with early language difficulty develop reading disorder, and 55% of children with reading disorder have a history of impaired early oral language development. By the time they enter kindergarten, many children with early language deficits may have improved significantly, and they may begin to show early literacy skills, identifying and sounding out letters. However, as they progress through school, they are often unable to keep up with the increasing demands for both oral and written language. Despite their ability to read words, these children lack oral and reading comprehension and struggle with a wide range of academic subjects. This “illusory recovery” of early language skill may result in children losing speech–language services or other special education support in early grades only to be identified later with academic problems. In addition, children with subtle, but persisting language impairments may appear inattentive or anxious in language-rich classroom environments and be misdiagnosed as having an attention disorder.

A study from Australia found that at 7–9 yr of age, children with communication impairments were reported by their parents and teachers to be making slower progress in reading, writing, and overall school achievement than other children their age. The children reported a higher incidence of bullying, poorer peer relationships, and less overall enjoyment of school than their typically developing peers.

COMORBID DISORDERS

Emotional and Behavioral Difficulty
Early language disorder, particularly difficulty with auditory comprehension, appears to be a specific risk factor for later emotional dysfunction. Boys and girls with language disorder have a higher than expected rate of anxiety disorder (principally social phobia). Boys with language disorder are more likely to develop symptoms of ADHD, conduct disorder, and antisocial personality disorder compared with normally developing peers. Language disorders are common in children referred for psychiatric services, but they are often underdiagnosed, and their impact on children's behavior and emotional development is often overlooked.

Preschoolers with language difficulty commonly express their frustration through anxious, socially withdrawn, or aggressive behavior. As their ability to communicate improves, parallel improvements are usually noted in their behavior, suggesting a cause-and-effect relationship between language and behavior. However, the persistence of emotional and behavioral problems over the life span of persons with early language disability suggests a strong biologic or genetic connection between language development and subsequent emotional disorders.

The full impact of environmental and education support on these emotional and behavioral difficulties is not known at this time, but many children with SLI need psychologic support. Efforts should be made to support the child's resilience, emotional competency, and coping abilities. Parents and teachers should be encouraged to strengthen the child's prosocial behavior and to reduce noncompliant and aggressive behaviors.

Motor and Coordination Delays
Approximately one-third to one-half of children with speech and/or language disorders have some degree of motor coordination impairment that may have an important impact on their ability to carry out activities of daily living (dressing, eating, and bathing), school tasks (writing, drawing, coloring), and social/recreational activities (participation in sports and other playground activities). Motor difficulties are not related to the type of language impairment (i.e., they are found in both children with only receptive delays and in those with both expressive and receptive delays). The patterns of motor difficulties seen in children with language impairments are not distinctly “abnormal” and the motor profiles of children with language impairments resemble those of younger children, suggesting that they result from delayed maturation of motor development rather than from a neurologic impairment. Several researchers have postulated that language impairments and motor difficulties may have a common neurodevelopmental basis. Because attention may be focused on the child's language delays, the need for intervention and support for the child's comorbid motor impairment may be overlooked.

Bibliography is available at Expert Consult.
Chapter 35  Language Development and Communication Disorders  214.e1

Bibliography


35.1 Childhood-Onset Fluency Disorder: Dysfluency (Stuttering, Stammering)

Kenneth L. Grizzle

Fluent speech requires timely synchronization of phonatory and articulatory muscle groups. There is also an important interaction between speech and language skills. Stuttering involves involuntary frequent repetitions, lengthenings (prolongations) or arrests (blocks, pauses) of syllables, or sounds that are exacerbated by emotionally or syntactically demanding speech. The World Health Organization’s definition of stuttering is a disorder in the rhythm of speech in which the person knows precisely what he or she wishes to say but at the same time may have difficulty saying it because of an involuntary repetition, prolongation, or cessation of sound. Table 35-4 describes the DSM-5 definition. Stuttering often leads to frustration and avoidance of speaking situations. Stuttering can lead to being bullied or teased and to speech-related anxiety and social phobia.

Epidemiology and Etiology

Stuttering usually begins at 2-4 yr of age and is seen more often in boys (4:1). Approximately 3-5% of preschool children stutter to some degree; only 0.7-1% of young adults stutter. Stuttering is common in families. Genetic studies suggest genes located on chromosome 12. Stuttering may occur suddenly and often begins when word combinations are involved. Higher vocabulary at age 2 yr and higher material education may also be associated with stuttering. Girls and those with a family history of recovery are most likely to have spontaneous recovery by adolescence. This recovery is not related to the severity of the stuttering. Approximately 75% of boys stop stuttering by adolescence; approximately 90% of girls stop by adolescence.

Adolescent/young adult onset stuttering may be related to central nervous system pathology. In contrast to childhood onset, adolescents may have dysfluency with each word whereas childhood onset usually manifests stuttering on the first word or syllable of a phrase.

Stuttering may be caused by impaired timing between areas of the brain involved in language preparation and execution. Adults who stutter and those with fluent speech activate similar areas of the brain. In addition, adults who stutter overactivate parts of the motor cortex and cerebellar vermis, show right-sided laterality, and have no auditory activation on hearing their own speech.

Table 35-5 Differences Between Stuttering and Developmental Dysfluency

<table>
<thead>
<tr>
<th>BEHAVIOR</th>
<th>STUTTERING</th>
<th>DEVELOPMENTAL DYSFLUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of syllable repetition per word</td>
<td>≥2</td>
<td>≤1</td>
</tr>
<tr>
<td>Tempo</td>
<td>Faster than normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Airflow</td>
<td>Often interrupted</td>
<td>Rarely interrupted</td>
</tr>
<tr>
<td>Vocal tension</td>
<td>Often apparent</td>
<td>Absent</td>
</tr>
<tr>
<td>Frequency of prolongations per 100 words</td>
<td>≥2</td>
<td>≤1</td>
</tr>
<tr>
<td>Duration of prolongation</td>
<td>≥2 sec</td>
<td>≤1 sec</td>
</tr>
<tr>
<td>Tension</td>
<td>Often present</td>
<td>Absent</td>
</tr>
<tr>
<td>Silent pauses within a word</td>
<td>May be present</td>
<td>Absent</td>
</tr>
<tr>
<td>Silent pauses before a speech attempt</td>
<td>Unusually long</td>
<td>Not marked</td>
</tr>
<tr>
<td>Silent pauses after the dysfluency</td>
<td>May be present</td>
<td>Absent</td>
</tr>
<tr>
<td>Articulating postures</td>
<td>May be inappropriate</td>
<td>Appropriate</td>
</tr>
<tr>
<td>Reaction to stress</td>
<td>More broken words</td>
<td>No change in dysfluency</td>
</tr>
<tr>
<td>Frustration</td>
<td>May be present</td>
<td>Absent</td>
</tr>
<tr>
<td>Eye contact</td>
<td>May waver</td>
<td>Normal</td>
</tr>
</tbody>
</table>


Additional disorders in the

Table 35-4 Childhood-Onset Fluency Disorder (Stuttering)

<table>
<thead>
<tr>
<th>Diagnostic Criteria</th>
<th>Childhood-Onset Fluency Disorder (Stuttering)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.</td>
<td>Disturbances in the normal fluency and time patterning of speech that are inappropriate for the individual’s age and language skills, persist over time, and are characterized by frequent and marked occurrences of one (or more) of the following:</td>
</tr>
<tr>
<td>1.</td>
<td>Sound and syllable repetitions.</td>
</tr>
<tr>
<td>2.</td>
<td>Sound prolongations of consonants as well as vowels.</td>
</tr>
<tr>
<td>3.</td>
<td>Broken words (e.g., pauses within a word).</td>
</tr>
<tr>
<td>4.</td>
<td>Audible or silent blocking (filled or unfilled pauses in speech).</td>
</tr>
<tr>
<td>5.</td>
<td>Circumlocutions (word substitutions to avoid problematic words).</td>
</tr>
<tr>
<td>6.</td>
<td>Words produced with an excess of physical tension.</td>
</tr>
<tr>
<td>7.</td>
<td>Monosyllabic whole-word repetitions (e.g., “I-I-I-I see him”).</td>
</tr>
<tr>
<td>B.</td>
<td>The disturbance causes anxiety about speaking or limitations in effective communication, social participation, or academic or occupational performance, individually or in any combination.</td>
</tr>
<tr>
<td>C.</td>
<td>The onset of symptoms is in the early developmental period.</td>
</tr>
<tr>
<td>D.</td>
<td>The disturbance is not attributable to a speech-motor or sensory deficit, dysfluency associated with neurological insult (e.g., stroke, tumor, trauma), or another medical condition and is not better explained by another mental disorder.</td>
</tr>
</tbody>
</table>

differential diagnosis include hearing impairment, medication effects, cluttering, and in adolescent onset stuttering, central nervous system disorders.

**TREATMENT**

Preschool children with normal developmental dysfluency (see Table 35-6) can be observed with parental education and reassurance. Parents should not reprimand the child or create undue anxiety. Preschool or older children with stuttering should be referred to a speech pathologist. Therapy is most effective if started during the preschool period. In addition to the risks noted in Table 35-4, indications for referral include 3 or more dysfluencies per 100 syllables (b-b-but; th-th-the; you, you, you), avoidances or escapes (pauses, head nod, blinking), discomfort or anxiety while speaking, and suspicion of an associated neurologic or psychotic disorder.

Most preschool children respond to interventions taught by speech pathologists and to behavioral feedback by parents. Parents should not yell at the child, but should calmly praise periods of fluency (“That was smooth”) or nonjudgmentally note episodes of stuttering (“That was a bit bumpy”). The child can be involved with self-correction and respond to requests (“Can you say that again?”) made by a calm parent. Such treatment greatly improves dysfluency but it may never be completely eliminated.

Adolescents and adults have also been treated (off label) with risperidone or olanzapine with varying but usually positive results if behavioral speech therapy is unsuccessful. Speech therapy in adolescents may be different from that in young children and involves speech restructuring with the development of a new speech pattern.

*Bibliography is available at Expert Consult.*

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**Table 35-6 Examples of Normal Dysfluency in Preschoolers**

<table>
<thead>
<tr>
<th>TYPE OF DYSFLUENCY</th>
<th>EXAMPLES</th>
</tr>
</thead>
</table>
| Voiced repetitions | Occasionally 2 word parts (mi…milk)  
Single-syllable words (I…I see you)  
Multisyllabic words (Barney…Barney is coming!)  
Phrases (I want…I want Elmo.) |
| Interjections       | We went to the…uh…cottage. |
| Revisions: incomplete phrases | I lost my….Where is Daddy going? |
| Prolongations       | I am Toooommy Baker. |
| Tense pauses        | Lips together, no sound produced |

Bibliography
Intellectual disability refers to a group of disorders that have in common deficits of adaptive and intellectual function and an age of onset before maturity is reached.

**DEFINITION**

Contemporary conceptualizations of intellectual disability emphasize functioning and social interaction rather than test scores. The definition of intellectual disability by the World Health Organization (WHO), the American Psychiatric Association (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-5]) and the American Association on Intellectual and Developmental Disabilities (AAIDD) all include significant impairment in general intellectual function, social skills, and adaptive behavior. This focus on the conceptual, social, and practical enables the development of individual treatment plans designed to enhance functioning. Consistent across these definitions is onset of symptoms before age 18 yr or adulthood or during childhood, even if the diagnosis is made later in life.

Significant impairment in general intellectual function refers to performance on an individually administered test of intelligence that is approximately 2 SD below the mean. For a test that has a mean of 100 and SD of 15, IQ scores below 70 would meet these criteria. If the standard error of measurement is considered, the upper limits of subaverage intellectual function may extend to an IQ of 75. Using a score of 75 to delineate intellectual disability might double the number of children with intellectual disability, but the requirement for impairment of adaptive skills limits the false positives. Children with intellectual disability often show a variable pattern of strengths and weaknesses. Not all of their partial scores on IQ tests fall into the significantly subaverage range.

Significant impairment in adaptive behavior reflects the degree that the cognitive dysfunction impairs daily function. Adaptive behavior refers to the skills that are required for people to function in their everyday lives. The AAIDD and DSM-5 classifications of adaptive behavior addresses 3 broad sets of skills: conceptual, social, and practical. Conceptual skills include language, reading and writing, money concepts, and self-direction. Social skills include interpersonal skills, personal responsibility, self-esteem, gullibility, naiveté, and ability to follow rules, obey laws, and avoid victimization. Representative practical skills are performance of activities of daily living (dressing, feeding, toileting and bathing, mobility), instrumental activities of daily living (e.g., housework, managing money, taking medication, shopping, preparing meals, using the telephone), occupational skills, and the maintenance of a safe environment. For a deficit in adaptive behavior to be present, a significant delay in 1 of the 3 areas must be present. The rationale for requiring only 1 of the 3 areas is the empirically derived finding that people with intellectual disability can have varying patterns of ability and may not have deficits in all 3 areas.

The requirement for adaptive behavior deficits is the most controversial aspect of the diagnostic formulation. The controversy centers on 2 broad areas: whether impairments in adaptive behavior are necessary for the construct of intellectual disability and what to measure. The adaptive behavior criterion may be irrelevant for many children; adaptive behavior is impaired in virtually all children who have IQ scores <50. The major utility of the adaptive behavior criterion is to confirm intellectual disability in children with IQ scores in the 65-75 range. It should be noted that deficits in adaptive behavior are often found in disorders such as autism spectrum disorders (see Chapter 30) and attention-deficit/hyperactivity disorder (ADHD) (see Chapter 33) in the presence of typical intellectual function.

The issues of measurement are important as well. The independence of the 3 domains of adaptive behavior has not been validated with research. The relationship between adaptive behavior and IQ performance is insufficiently explored. Most adults with mild intellectual disability do not have significant impairments in practical skills. It should be noted that adaptive behavior deficits must be distinguished from maladaptive behavior (e.g., aggression, inappropriate sexual contact).

Onset before age 18 yr or adulthood distinguishes dysfunctions that originate during the developmental period. The diagnosis of intellectual disability may be made after 18 yr of age or childhood, but the cognitive and adaptive dysfunction must have been manifested before age 18 or adulthood (e.g., during “childhood”).

The term mental retardation should be cast aside because it is stigmatizing, has been used to limit the achievements of the individual, and has not met its initial objective of providing assistance to people with the disorder. The term intellectual disability is increasingly used...
in its place, but has not been adopted universally. In the United States, some existing laws and their attendant entitlements still use the term mental retardation. In Europe, the term learning disability is often used to describe intellectual disability. Global developmental delay is a term often used to describe young children whose limitations have not yet resulted in a formal diagnosis of intellectual disability; it is often inappropriately used beyond the point when it is clear the child has intellectual disability, usually age 3 yr. Developmental delay is a classification that may be used by IDEA until age 9 yr.

**ETIOLOGY**

There appear to be 2 overlapping populations of children with intellectual disability: mild (IQ 50-70), which is more associated with environmental influences, and severe (IQ <50), which is more frequently linked to biologic and genetic causes. Mild intellectual disability is 4 times more likely to be found in the offspring of women who have not completed high school than in women who have graduated. This is presumably a consequence of both genetic (children can inherit an intellectual impairment) and socioeconomic (poverty, malnutrition) factors. The specific causes of mild intellectual disability are identifiable in <50% of affected individuals. The most common biologic causes of mild intellectual disability include genetic or chromosomal syndromes with multiple, major, or minor congenital anomalies (velocardiofacial syndrome, Williams syndrome, Noonan syndrome), intrauterine growth restriction, prematurity, perinatal insults, intrauterine exposure to drugs of abuse (including alcohol), and sex chromosomal abnormalities. Familial clustering is common.

In children with severe intellectual disability, a biologic cause (most commonly prenatal) can be identified in more than 75% of cases. Causes include chromosomal (e.g., Down syndrome Wolf-Hirschhorn syndrome, deletion 1p36 syndrome) and other genetic and epigenetic disorders (e.g., fragile X syndrome, Rett syndrome, Angelman and Prader-Willi syndromes), abnormalities of brain development (e.g., lissencephaly), and inborn errors of metabolism or neurodegenerative disorders (Table 36-1). Nonsyndromic severe intellectual disability may be a result of inherited or de novo gene mutations, as well as microdeletions or microduplications not detected on standard chromosome analysis. More than 400 genes may be associated with nonsyndromic intellectual disability, with many detected by exomic sequencing. These de novo point mutations may also cause other phenotype features such as seizures or autism; the absence of these features suggests more pleotropic manifestations of genetic mutations. Consistent with the finding that disorders that alter early embryogenesis are the most common and severe, the earlier the problem occurs in development, the more severe its consequences tend to be.

**EPIDEMIOLOGY**

The prevalence of intellectual disability depends on the definition, the method of ascertainment, and the population. According to statistics, 2.5% of the population should have intellectual disability, and 75% of these individuals should fall into the mild to moderate range. Rates vary across populations. Globally, the prevalence of intellectual disability has been estimated to be approximately 16.41/1,000 persons in low income countries, approximately 15.94/1,000 for middle-income countries, and approximately 9.21/1,000 in high-income countries. Overall, intellectual disability occurs more in boys than in girls: 2:1 in mild intellectual disability and 1.5:1 in severe intellectual disability. In part this may be a consequence of the many X-linked disorders associated with intellectual disability, the most prominent being fragile X syndrome (see Chapter 81.5).

In 2009-2010 in the United States, approximately 463,000 or 0.9% of school-age children received services for intellectual disability in federally supported school programs. For several reasons, fewer children than predicted are identified as having mild intellectual disability. Because it is more difficult to diagnose mild intellectual disability than the more severe forms, professionals might defer the diagnosis and give the benefit of the doubt to the child. Other reasons that contribute to the discrepancy are use of instruments that underidentify young children with mild intellectual disability (Chapter 30), some children being diagnosed as having autism spectrum disorders and their intellectual disability not addressed, and a disinclination to make the diagnosis in poor or minority students because of previous overdiagnosis. Young children might show cognitive limitations without significant delays in adaptive behavior. As a result, new cases of mild intellectual disability continue to be diagnosed among children up to 9 yr of age. Children with intellectual disability also may be incorporated into another diagnosis (e.g., autism, cerebral palsy). Furthermore, it

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**Table 36-1** Identification of Cause in Children with Severe Intellectual Disability

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>EXAMPLES</th>
<th>PERCENT OF TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomal disorder</td>
<td>Trisomies 21, 18, 13, Deletion 1p36, Klinefelter syndrome, Wolf-Hirschhorn syndrome</td>
<td>~20</td>
</tr>
<tr>
<td>Genetic syndrome</td>
<td>Fragile X syndrome, Prader-Willi syndrome, Rett syndrome</td>
<td>~20</td>
</tr>
<tr>
<td>Nonsyndromic autosomal mutations</td>
<td>Variations in copy number, de novo mutations in SYNGAP1, GRIK2, TUSC3, oligosaccharyl transferase, and others</td>
<td>~10</td>
</tr>
<tr>
<td>Developmental brain abnormality</td>
<td>Hydrocephalus ± meningomyelole, lissencephaly</td>
<td>~8</td>
</tr>
<tr>
<td>Inborn errors of metabolism or neurodegenerative disorder</td>
<td>PKU, Tay-Sachs, various storage diseases</td>
<td>~7</td>
</tr>
<tr>
<td>Congenital infections</td>
<td>HIV, toxoplasmosis, rubella, CMV, syphilis, herpes simplex</td>
<td>~3</td>
</tr>
<tr>
<td>Familial intellectual disability</td>
<td>Environment, syndromic, or genetic</td>
<td>~5</td>
</tr>
<tr>
<td>Perinatal causes</td>
<td>HIE, meningitis, IVH, PVL, fetal alcohol syndrome</td>
<td>4</td>
</tr>
<tr>
<td>Postnatal causes</td>
<td>Trauma (abuse), meningitis, hypothyroidism</td>
<td>~4</td>
</tr>
<tr>
<td>Unknown</td>
<td>Cerebral palsy</td>
<td>20</td>
</tr>
</tbody>
</table>

CMV, Cytomegalovirus; HIE, hypoxic ischemic encephalopathy; HIV, human immunodeficiency virus; IVH, intraventricular hemorrhage; PKU, phenylketonuria; PVL, periventricular leukomalacia.

is possible that the number of children with mild intellectual disability is actually decreasing as a result of public health and education measures to prevent prematurity and provide early intervention and head start programs. In fact, the number of school children who receive services for intellectual disability has decreased since 1999, but if developmental delay is included, the numbers have not changed appreciably.

Unlike mild intellectual disability, where the prevalence may be decreasing, the occurrence of severe intellectual disability has not changed appreciably since the 1940s and is 0.3-0.5% of the population. Many of the causes of severe intellectual disability involve genetic or congenital brain malformations that can neither be anticipated nor treated at present. In addition, new populations with severe intellectual disability have offset the decreases in the prevalence of severe intellectual disability that have resulted from improved healthcare. Although prenatal diagnosis and subsequent pregnancy terminations have resulted in a decreased prevalence of Down syndrome (see Chapter 81), and newborn screening with early treatment has virtually eliminated intellectual disability caused by phenylketonuria and congenital hypothyroidism, an increased prevalence of maternal prenatal drug use (see Chapter 96.4) and improved survival of very-low-birthweight premature infants has counterbalanced this effect.

### PATHOLOGY AND PATHOGENESIS

The limitations in our knowledge of the neuropathology of intellectual disability are exemplified by the fact that 10-20% of brains of persons with severe intellectual disability appear entirely normal by standard neuropathologic study. The majority of brains of these persons show only mild, nonspecific changes that correlate poorly with the degree of intellectual disability. These changes include microcephaly, gray matter heterotopias in the subcortical white matter, unusually regular columnar arrangement of the cortex, and neurons that are more tightly packed than usual. Only a minority of the brain shows more specific changes in dendritic and synaptic organization, with dysgenesis of dendritic spines or cortical pyramidal neurons, or impaired growth of dendritic trees. The programming of the central nervous system (CNS) involves a process of induction; CNS maturation is defined in terms of genetic, molecular, autocrine, paracrine, and endocrine influences. Receptors, signaling molecules, and genes are critical to brain development. The maintenance of different neuronal phenotypes in the adult brain involves the same genetic transcripts that play a crucial role during fetal development, with activation of similar intracellular signal transduction mechanisms. Several syndromes that were thought to involve complex chromosomal abnormalities are, in fact, caused by single-gene mutations involving induction. Rubinstein-Taybi syndrome (see Chapter 81), a disorder marked clinically by broad thumbs and great toes, characteristic facies, and severe intellectual disability, results from a mutation in the gene encoding for the transcriptional coactivator CREB-binding protein (CBP), a factor important in the control of gene expression in early embryogenesis.

### CLINICAL MANIFESTATIONS

Early diagnosis of intellectual disability facilitates earlier intervention, identification of abilities, realistic goal setting, easing of parental anxiety, and greater acceptance of the child in the community. Most children with intellectual disability first come to the pediatrician's attention in infancy because of dysmorphisms, associated developmental disabilities, or failure to meet age-appropriate developmental milestones. There are no specific physical characteristics of intellectual disability, but dysmorphisms may be the earliest signs that bring children to the attention of the pediatrician. They might fall within a genetic syndrome such as Down syndrome or be isolated, as in microcephaly or failure to thrive. Associated developmental disabilities include seizure disorders, cerebral palsy, hypotonia, and autism; these conditions are seen more commonly in conjunction with intellectual disability than in the general population.

Most children with intellectual disability do not keep up with their peers and fail to meet age-appropriate norms. In early infancy, failure to meet age-appropriate expectations can include a lack of visual or auditory responsiveness, unusual muscle tone (hypo- or hypertonia) or posture, and feeding difficulties. Between 6 and 18 mo of age, gross motor delay (lack of sitting, crawling, walking) is the most common complaint. Language delay and behavior problems are common concerns after 18 mo (Table 36-2). Earlier identification of atypical development is likely to occur with more severe impairments; and intellectual disability is usually identifiable by age 3 yr.

For some children with mild intellectual disability the diagnosis remains uncertain during the early school years. It is only after the demands of the school setting increase over the years, changing from “learning to read” to “reading to learn,” that the child’s limitations are clarified.

Adolescents with mild intellectual disability can present a diagnostic challenge. Typically they are up to date on current trends and are conversant as to who, what, and where. It isn’t until the “why” and “how” questions are asked that their limitations become apparent. If allowed to interact at a superficial level, their mild intellectual disability might not be appreciated, even by professionals who may be their special education teachers or healthcare providers. Because of the stigma associated with intellectual disability, they may use euphemisms to avoid being thought of as “stupid” or “retarded” and refer to themselves as learning disabled, dyslexic, language disordered, or slow learners. Some people with intellectual disability emulate their social milieu to be accepted. They may be social chameleons and assume the morals of the group to which they are attached. Some would rather be thought “bad” than “incompetent.”

### LABORATORY FINDINGS

The most commonly used medical diagnostic testing for children with intellectual disability include neuroimaging: metabolic, genetic, and chromosomal testing; microarray analysis; and electroencephalography. These tests should not be used as screening tools for all children with an intellectual disability. In some children, there is a reasonable yield for testing, whereas in others the yield of <1% does not support its use. Decisions on diagnostic testing should be based on the medical and family history, physical examination, testing by other disciplines, and the family’s wishes. Table 36-3 summarizes clinical practice guidelines that have been published and the yields of testing to assist in evaluating the child with global developmental delay or intellectual disability. Microarray analysis has replaced karyotyping as the preferred approach for children with multiple abnormalities or a positive family history. Microarray analysis has the ability to discern abnormalities that are below the resolution of karyotyping. For example, deletion 1p36 syndrome, the most common subtelomeric microdeletion syndrome (1:5,000 births), accounts for approximately 1% of

<table>
<thead>
<tr>
<th>AGE</th>
<th>AREA OF CONCERN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>Dymorphic syndromes, (multiple congenital anomalies), microcephaly Major organ system dysfunction (e.g., feeding and breathing)</td>
</tr>
<tr>
<td>Early infancy (2-4 mo)</td>
<td>Failure to interact with the environment Concerns about vision and hearing impairments</td>
</tr>
<tr>
<td>Later infancy (6-18 mo)</td>
<td>Gross motor delay</td>
</tr>
<tr>
<td>Toddlers (2-3 yr)</td>
<td>Language delays or difficulties</td>
</tr>
<tr>
<td>Preschool (3-5 yr)</td>
<td>Language difficulties or delays Behavior difficulties, including play Delays in fine motor skills: cutting, coloring, drawing</td>
</tr>
<tr>
<td>School age (&gt;5 yr)</td>
<td>Academic underachievement Behavior difficulties (attention, anxiety, mood, conduct, etc.)</td>
</tr>
</tbody>
</table>
children with developmental disabilities and is characterized by failure to thrive, microcephaly, deep-set eyes, midface hypoplasia, broad nasal bridge, heart defects, and CNS anomalies. Noncompaction cardiomyopathy and seizures are also noted. The diagnosis is made by standard chromosomes in only approximately 20% and requires fluorescent in situ hybridization or microarray comparative genomic hybridization methods for remaining patients. Microarray analysis may identify variants of unknown significance or benign variants, and therefore should be used in conjunction with a genetic consultation. Karyotyping has a role for children whose array analysis is unrevealing and concern is present for inversions, balanced insertions, and reciprocal translocations. Fluorescent in situ hybridization and subtelomeric analysis have been largely replaced by microarray analysis but continue to be used for specific indications. If microarray analysis is not diagnostic whole exome sequencing increases the diagnostic yield in many children with nonsyndromic severe intellectual disability.

Molecular genetic testing for fragile X syndrome is appropriate for a boy with moderate intellectual disability, unusual physical features, and/or a family history of intellectual disability, or for a girl with more subtle cognitive deficits associated with severe shyness and a relevant family history. For children with a strong history of X-linked intellectual disability, specific testing of genes or the entire chromosome may be revealing. MECP2 (methyl CpG binding protein 2 [Rett syndrome]) testing should be considered in girls with moderate to severe disability.

A child with a progressive neurologic disorder, developmental regression, or acute behavioral changes needs metabolic investigation (urinary organic acids, plasma amino acids, lactate, lysosomal enzymes in lymphocytes), although many of these disorders are detectable as part of newborn screening; a child with seizure-like episodes should have an electroencephalography performed. Children with micro- or macrocephaly or changes in head growth trajectory or asymmetric head shapes, as well as those with new or focal neurologic findings, including seizures, should have a neuroimaging procedure.

MRI scans identify a significant number of subtle markers of cerebro dysgenesis in children with intellectual disability. Formes frustes

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**Table 36-3  Suggested Evaluation of the Child with Intellectual Disability/Global Developmental Delay**

<table>
<thead>
<tr>
<th>TEST</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-depth history</td>
<td>Includes pre-, peri-, and postnatal events (including seizures); developmental attainments; and 3-generation pedigree in family history</td>
</tr>
<tr>
<td>Physical examination</td>
<td>Particular attention to minor or subtle abnormalities; neurologic examination for focality and skull abnormalities Behavioral phenotype</td>
</tr>
<tr>
<td>Vision and hearing evaluation</td>
<td>Essential to detect and treat; can mask as developmental delay</td>
</tr>
<tr>
<td>Gene microarray analysis</td>
<td>A 7.8% yield overall (10% in syndromic and 6.5% in nonsyndromic intellectual disability) Better resolution than Karyotype. May identify up to twice as many abnormalities as karyotyping. Excellent in detecting de novo microdeletions or microduplications</td>
</tr>
<tr>
<td>Karyotype</td>
<td>Yield 4% in global developmental delay/intellectual disability Best for inversions and balanced insertions, reciprocal translocations, and polyploidy</td>
</tr>
<tr>
<td>Fragile X screen</td>
<td>Combined yield 2% Preselection on clinical grounds can increase yield to 7.6%</td>
</tr>
<tr>
<td>X-linked candidate intellectual disability genes</td>
<td>May explain up to 10% of intellectual disability Yield may be as high as 42% if there is a definite family history and as high as 17% from a possibly linked kindred</td>
</tr>
<tr>
<td>Exomic gene sequencing</td>
<td>Detects inherited and de novo point mutations especially in nonsyndromic severe intellectual disability</td>
</tr>
<tr>
<td>Neuroimaging</td>
<td>MRI preferred. Positives increased by abnormalities of skull contour or microcephaly and macrocephaly, or focal neurologic examination. Overall has a higher yield Identification of specific etiologies is rare. Most conditions that are found do not alter the treatment plan. Need to weigh risk of sedation against possible yield</td>
</tr>
<tr>
<td>Thyroid (T&lt;sub&gt;4&lt;/sub&gt;, TSH)</td>
<td>Near 0% in settings with universal newborn screening program</td>
</tr>
<tr>
<td>Serum lead</td>
<td>If there are identifiable risk factors for excessive environmental lead exposure</td>
</tr>
<tr>
<td>Metabolic testing</td>
<td>Yield 0.2-4.6% based on clinical indicators and tests performed Urine organic acids, plasma amino acids, ammonia, lactate, and a capillary blood gas. Focused testing based on clinical findings is warranted Tandem mass spectrometry newborn screening has allowed for identification of many disorders in perinatal period and have decreased yield in older children. Other disorders have emerged; e.g., congenital disorders of glycosylation and disorders of creatine synthesis and transport</td>
</tr>
<tr>
<td>MECP2 for Rett syndrome</td>
<td>1.5% of females with severe intellectual disability 0.5% of males</td>
</tr>
<tr>
<td>EEG</td>
<td>May be deferred in absence of history of seizures</td>
</tr>
<tr>
<td>Repeated history and physical examination</td>
<td>Can give time for maturation of physical and behavioral phenotype. New technology may be available for evaluation</td>
</tr>
</tbody>
</table>

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**Notes:**

EEG, Electroencephalogram; CGH, comparative genomic hybridization; MECP2, methyl CpG binding protein 2; T<sub>4</sub>, thyroxine; TSH, thyroid-stimulating hormone.

Part IV – Learning Disorders

of amino acid and organic acid disorders are associated with intellectual disability in the absence of the more commonly associated manifestations of behavior change, lethargy, and coma.

Some children with more subtle physical or neurologic findings can also have determinable biologic causes of their intellectual disability (see Chapter 83). How intensively one investigates the cause of a child’s intellectual disability is based on a number of factors:

◆ What is the degree of intellectual disability? One is less likely to find a biologic cause in a child with mild intellectual disability than in a child with a severe intellectual disability.

◆ Is there a specific diagnostic path to follow? If there is a medical history or a family history, or if physical findings pointing to a specific disorder, a diagnosis is more likely to be made. In the absence of these indicators, it is difficult to choose specific tests to perform.

◆ Are the parents planning on having additional children? If so, one would be more likely to intensively seek disorders for which prenatal diagnosis or a specific early treatment option is available.

◆ What are the parents’ wishes? Some parents have little interest in searching for the cause of the intellectual disability and focus exclusively on treatment. Others are so focused on obtaining a diagnosis that they have difficulty following through on interventions until a cause has been found. The entire spectrum of responses must be respected, and supportive guidance should be provided in the context of the parents’ education.

DIFFERENTIAL DIAGNOSIS

One of the important roles of pediatrics is the early recognition and diagnosis of cognitive deficits. The developmental surveillance approach to early diagnosis of intellectual disability should be multifaceted. Parents’ concerns and observations about their child’s development should be listened to carefully, because their observations have been found to be as accurate as developmental screening tests. Medical, genetic, and environmental risk factors should be recognized. Infants at high risk (prematurity, maternal substance abuse, perinatal insult) should be registered in newborn follow-up programs in which they are evaluated periodically for developmental lags in the first 2 yr of life; they should be referred to early intervention programs as appropriate. Developmental milestones should be recorded routinely during healthcare maintenance visits. The American Academy of Pediatrics has formulated a schema for developmental surveillance and screening. Whether developmental surveillance is a more effective technique for identifying than recognizing failure to meet age-appropriate milestones has not been clearly established.

Before making the diagnosis of intellectual disability, other disorders that affect cognitive abilities and adaptive behavior should be considered. These include conditions that mimic intellectual disability and others that involve intellectual disability as an associated impairment. Sensory deficits (severe hearing and vision loss), communication disorders, and poorly controlled seizure disorders can mimic intellectual disability; certain progressive neurologic disorders can appear as intellectual disability before regression is appreciated. More than half of children with cerebral palsy (see Chapter 598) or autism spectrum disorders (see Chapter 30) also have intellectual disability as an associated deficit. Differentiation of isolated cerebral palsy from intellectual disability relies on motor skills being more affected than cognitive skills and on the presence of pathologic reflexes and tone changes. In autism spectrum disorders, language and social adaptive skills are more affected than nonverbal reasoning skills, whereas in intellectual disability there are usually more equivalent deficits in social, fine motor, adaptive, and cognitive skills.

DIAGNOSTIC PSYCHOLoGIC TESTING

The formal diagnosis of intellectual disability requires the administration of individual tests of intelligence and adaptive functioning. The Bayley Scales of Infant Development (BSID-III), the most commonly used infant intelligence scale, assesses language, visual problem-solving skills, behavior, fine motor skills, and gross motor skills in children between 1 mo and 42 mo of age. A Mental Developmental Index (MDI) and a Psychomotor Development Index (PDI, a measure of motor competence) score are derived from the results. This test permits the differentiation of infants with severe intellectual disability from typically developing infants, but it is less helpful in distinguishing between a typical child and one with mild intellectual disability.

The most commonly used psychologic tests for children older than 3 yr of age are the Wechsler Scales. The Wechsler Preschool and Primary Scale of Intelligence, 4th edition (WPPSI-IV) is used for children with mental ages of 2.5–7.6 yr. The Wechsler Intelligence Scale for Children, 4th edition (WISC-IV), is used for children who function above a 6 yr mental age. Both scales contain a number of subtests in the areas of verbal and performance skills. Although children with intellectual disability usually score below average on all subscale scores, they occasionally score in the average range in 1 or more performance areas.

The most commonly used test of adaptive behavior is the Vineland Adaptive Behavior Scale (VABS), which involves semi structured interviews with parents and/or caregivers and teachers that assess adaptive behavior in four domains: communication, daily living skills, socialization, and motor skills. Other tests of adaptive behavior include the Woodcock-Johnson Scales of Independent Behavior–Revised, the American Association on Intellectual and Developmental Disability Adaptive Behavior Scale (ABS-2nd edition), and the Adaptive Behavior Assessment System (ABAS-2nd edition). There is usually (but not always) a good correlation between scores on the intelligence and adaptive scales. Basic adaptive abilities (feeding, dressing, hygiene) are more responsive to remedial efforts than is the IQ score. Adaptive abilities are also more variable, which can relate to the underlying condition and to environmental expectations. Although persons with Prader-Willi syndrome (see Chapter 81) have stability of adaptive skills through adulthood, those with fragile X syndrome may have increasing deficits over time.

COMPLICATIONS

Children with intellectual disability have higher rates of vision, hearing, neurologic, orthopedic, and behavioral or emotional disorders than do typically developing children. These other problems are often detected later in children with intellectual disability. If untreated, the associated impairments can potentially adversely affect the individual’s outcome more than the intellectual disability itself.

The most common associated deficits are motor impairments, behavioral and emotional disorders, medical complications, and seizures. The more severe the intellectual disability, the greater are the number and severity of associated impairments. Knowing the cause of the intellectual disability can help predict which associated impairments are most likely to occur. Fragile X syndrome and fetal alcohol syndrome (see Chapter 106.2) are associated with a high rate of behavioral disorders; Down syndrome has many medical complications (hypothyroidism, celiac disease, congenital heart disease, atlantoaxial subluxation). Associated impairments can require ongoing physical therapy, occupational therapy, speech-language therapy, adaptive equipment, glasses, hearing aids, and medication. Failure to identify and treat these impairments adequately can hinder successful habilitation and result in difficulties in the school, home, and/or neighborhood environment.

PREVENTION

Examples of primary programs to prevent intellectual disability include:

◆ Increasing the public’s awareness of the adverse effects of alcohol and other drugs of abuse on the fetus
◆ Preventing teen pregnancy and promoting early prenatal care
◆ Preventing traumatic injury by encouraging the use of guards and railings to prevent falls and other avoidable injuries in the home; using appropriate seat restraints when driving and wearing a safety helmet when biking or skateboarding; teaching firearms safety
◆ Preventing poisonings by teaching parents about locking up medications and potential poisons
Encouraging safe sexual practices to prevent the transmission of diseases
Implementing immunization programs to reduce the risk of intellectual disability caused by encephalitis, meningitis, and congenital infection

Presymptomatic detection of certain disorders can result in treatment that prevents adverse consequences. State newborn screening by tandem mass spectrometry (now including >50 rare genetic disorders in most states), newborn hearing screening, and preschool lead poisoning prevention programs are examples. Thyroid screening in a child with Down syndrome is an example of presymptomatic testing in a disorder associated with intellectual disability.

**TREATMENT**

Although intellectual disability is not treatable, many associated impairments are amenable to intervention and therefore benefit from early identification. Most children with an intellectual disability do not have a behavioral or emotional disorder as an associated impairment, but challenging behaviors (aggression, self-injury, oppositional defiant behavior) and mental illness (mood and anxiety disorders) occur with greater frequency in this population than among children with typical intelligence. These behavioral and emotional disorders are the primary cause for out-of-home placements, reduced employment prospects, and decreased opportunities for social integration.

Some behavioral and emotional disorders are difficult to diagnose in children with more severe intellectual disability because of the child’s limited abilities to understand, communicate, interpret, or generalize. Other disorders are masked by the intellectual disability. The detection of ADHD (see Chapter 33) in the presence of moderate to severe intellectual disability may be difficult, as may be discerning a thought disorder (psychosis) in someone with autism and intellectual disability.

Although mental illness is generally of biologic origin and responds to medication, behavioral disorders can result from a mismatch between the child’s abilities and the demands of the situation, organic problems, and/or family difficulties. They may represent attempts by the child to communicate, gain attention, or avoid frustration. In assessing the challenging behavior, one must also consider whether it is inappropriate for the child’s mental age, rather than the chronological age. When intervention is needed, an environmental change, such as a more appropriate classroom setting, may improve certain behavior problems. Behavior management techniques are useful; psychopharmacologic agents may be appropriate in certain situations.

Medication is not useful in treating the core symptoms of intellectual disability; no agent has been found to improve intellectual function. Medication may be helpful in treating associated behavioral and psychiatric disorders. Psychopharmacology is generally directed at specific symptom complexes including ADHD (stimulant medication), self-injurious behavior and aggression (neuroleptics), and anxiety obsessive-compulsive disorder, and depression (selective serotonin reuptake inhibitors). Before long-term therapy with any psychopharmacologic agent is initiated, a short trial should be conducted. Even if a medication proves successful, its use should be reevaluated at least yearly to assess the need for continued treatment.

**SUPPORTIVE CARE AND MANAGEMENT**

Each child with intellectual disability needs a medical home with a pediatrician who is readily accessible to the family to answer questions, help coordinate care, and discuss concerns. Pediatricians can have effects on patients and their families that are still felt decades later. The role of the pediatrician includes involvement in prevention efforts, early diagnosis, identification of associated deficits, referral for appropriate diagnostic and therapeutic services, interdisciplinary management, provision of primary care, and advocacy for the child and family. The management strategies for children with an intellectual disability should be multimodal, with efforts directed at all aspects of the child’s life: health, education, social and recreational activities, behavior problems, and associated impairments. Support for parents and siblings should also be provided.

**Primary Care**

For children with an intellectual disability, primary care has a number of important components:

- Provision of the same primary care received by all other children of similar chronological age (see Chapter 35)
- Anticipatory guidance relevant to the child’s level of function: feeding, toileting, school, accident prevention, sexuality education
- Assessment of issues that are relevant to that child’s disorder: e.g., examination of the teeth in children who exhibit bruxism, thyroid function in children with Down syndrome, cardiac function in Williams syndrome (see Chapter 108)

The American Academy of Pediatrics has published a series of guidelines for children with specific genetic disorders associated with intellectual disability (Down syndrome, fragile X syndrome, and Williams syndrome). Goals should be considered and programs adjusted as needed during the primary care visit. Decisions should also be made about what additional information is required for future planning or to explain why the child is not meeting expectations. Other evaluations, such as formal psychologic or educational testing, may need to be scheduled.

**Interdisciplinary Management**

The pediatrician has the responsibility for consulting with other disciplines to make the diagnosis of intellectual disability and coordinate treatment services. Consultant services may include psychology, speech-language pathology, physical therapy, occupational therapy, audiology, nutrition, nursing, and/or social work, as well as medical specialties such as neurodevelopmental disabilities, neurology, genetics, psychiatry, developmental-behavioral pediatricians, and/or surgical specialties. Contact with early intervention and school personnel is equally important to help prepare the child’s Individual Family Service Plan/Individual Educational Plan. The family should be an integral part of the planning and direction of this process. Care should be family centered and culturally sensitive; for older children, their participation in planning and decision making should be promoted to whatever extent possible.

**Periodic Reevaluation**

The child’s abilities and the family’s needs change over time. As the child grows, more information must be provided to the child and family, goals must be reassessed, and programming needs should be adjusted. A periodic review should include information about the child’s health status as well as the child’s functioning at home, at school, and in other community settings. Other information, such as formal psychologic or educational testing, may be helpful. Reevaluation should be undertaken at routine intervals (6-12 mo during early childhood), at any time the child is not meeting expectations, or when the child is moving from one service delivery system to another. This is especially true during the transition to adulthood, beginning at age 14 yr as mandated by the IDEA Amendments of 2004. This transitioning should include the transfer of care to the adult healthcare system by age 21 yr.

**Educational Services**

Education is the single most important discipline involved in the treatment of children with an intellectual disability. The educational program must be relevant to the child’s needs and address the child’s individual strengths and weaknesses. The child’s developmental level, the child’s requirements for support, and goals for independence provide a basis for establishing an Individualized Education Program for school-age children, as mandated by federal legislation.

**Leisure and Recreational Activities**

The child’s social and recreational needs should be addressed. Although young children with intellectual disability are generally included in play activities with children who have typical development, adolescents with intellectual disability often do not have opportunities for appropriate social interactions. Participation in sports should be encouraged, even if the child is not competitive, because it offers many benefits.
including weight management, development of physical coordination, maintenance of cardiovascular fitness, and improvement of self-image. Social activities are equally important, including dances, trips, dating, and other typical social and recreational events.

**Family Counseling**

Many families adapt well to having a child with intellectual disability, but some have emotional or social difficulties. The risks of parents’ depression and child abuse and neglect are higher in this group of children than in the general population. Among the factors that have been associated with good family coping and parenting skills are stability of the marriage, good parental self-esteem, limited number of siblings, higher socioeconomic status, lower degree of disability or associated impairments, parents’ appropriate expectations and acceptance of the diagnosis, supportive extended family members, and availability of community programs and respite care services. In families in which the emotional burden of having a child with intellectual disability is great, family counseling, parent support groups, respite care, and home health services should be an integral part of the treatment plan.

**PROGNOSIS**

In children with severe intellectual disability, the prognosis is often evident by early childhood. Mild intellectual disability might not always be a lifelong disorder. Children might meet criteria for intellectual disability at an early age, but later the disability can evolve into a more specific developmental disorder (communication disorder, autism, slow learner, or borderline normal intelligence). Others with a diagnosis of mild intellectual disability during their school years develop sufficient adaptive behavior skills so that they no longer fit the diagnosis as adolescents, or the effects of maturation and plasticity can result in children moving from one diagnostic category to another (from moderate to mild retardation). Some children who have a diagnosis of a specific learning disability or communication disorder might not maintain their rate of cognitive growth and fall into the range of intellectual disability over time. By adolescence, the diagnosis has generally stabilized.

The apparent higher prevalence of intellectual disability in low and middle income group countries is of concern given the limitations in available resources. While community-based rehabilitation is being implemented in more than 90 countries, the efficacy of such programs has not been established.

The long-term outcome of persons with intellectual disability depends on the underlying cause, the degree of cognitive and adaptive deficits, the presence of associated medical and developmental impairments, the capabilities of the families, and the school and community supports, services, and training provided to the child and family (Table 36-4). As adults, many persons with mild intellectual disability are capable of gaining economic and social independence with functional literacy. They might need periodic supervision, especially when under social or economic stress. Most live successfully in the community, either independently or in supervised settings. Life expectancy is not adversely affected by intellectual disability itself.

For persons with moderate intellectual disability, the goals of education are to enhance adaptive abilities and “survival” academic and vocational skills so they are better able to live in the adult world (see Table 36-4). The concept of supported employment has been very beneficial to these individuals; the person is trained by a coach to do a specific job in the setting in which the person is to work. This bypasses the need for a sheltered workshop experience and has resulted in successful work adaptation in the community for many people with an intellectual disability. These persons generally live at home or in a supervised setting in the community.

As adults, people with severe to profound intellectual disability usually require extensive to pervasive supports (see Table 36-4). These individuals may have associated impairments, such as cerebral palsy, behavioral disorders, epilepsy, or sensory impairments, that further limit their adaptive functioning. They can perform simple tasks in supervised settings. Most people with this level of intellectual disability are able to live in the community with appropriate supports.

Bibliography is available at Expert Consult.
Chapter 36  Intellectual Disability  222.e1

Bibliography
American Academy of Pediatrics, Committee on Children with Disabilities: Pediatrician’s role in the development and implementation of an Individualized Education Plan (IEP) and/or an Individual Family Service Plan (IFSP), Pediatrics 104:124–127, 1999.
Adoption is a social, emotional, and legal process that provides a new family for a child when the birth family is unable or unwilling to parent. In the United States, about 1 million children <18 yr of age are adopted; 2-4% of all American families have adopted. Annually across the globe, approximately 250,000 children are adopted; approximately 30,000 of adoptions are between nations. In the United States approximately 136,000 children were adopted in 2008, a 15% increase since 1990. Of these, approximately 40% were stepparent or relative adoptions. Of non-stepparent adoptions, approximately 60% were from the child welfare system, 25% were international, and 15% were voluntarily adoption-placed domestic infants. Public agencies support approximately 50% of total annual adoptions in the United States, private agencies facilitate approximately 25% of adoptions, and independent practitioners, for example, lawyers, handle approximately 15% of adoptions. Compared to 19% of the general population, approximately 39% of adopted children have special healthcare needs.

The Adoption and Safe Families Act (P.L. 105-89) requires children in foster care to be placed with adoptive families if they cannot be safely returned to their families within a reasonable period of time. In fiscal year (FY) 2011, there were 104,236 children waiting for adoption, including 61,361 whose biological parents’ rights had been terminated. Many children awaiting adoption have “special needs” because they are of school age, part of a sibling group, members of historically oppressed racial/ethnic groups, or because they have considerable physical, emotional, or developmental needs. A number of policy efforts are aimed at increasing adoption opportunities for these children, including federal adoption subsidies, tax credits, recruitment efforts to identify ethnically diverse adults willing to adopt, increased preplacement services, and expanding adoption opportunities to single adults, gay/lesbian partners, and older couples.

Along with foster care adoptions, international adoptions are a way of providing stable, long-term care to vulnerable children throughout the world. There is concern that in some countries of origin the rapid growth of international adoption has outpaced regulation and oversight to protect vulnerable children/families. Opportunities for financial gain have led to abuses, including the sale and abduction of children, bribery, and financial coercion of families, though the extent and scope of the potential concern is difficult to ascertain. Increasing global efforts, such as the Hague Convention on Protection of Children and Co-operation in Respect of Intercountry Adoption, have promoted political cooperation between nations and established international law to reduce potential for child abduction/trafficking and to ensure that the best interests of the child are paramount in decision making. Participating nations, including the United States, are working to address the myriad sociopolitical conditions that create the need for out-of-family care, and are working to support children within their nations’ borders. International adoption is increasingly considered a measure of last resort if the child cannot be cared for within the child’s birth family (including extended relatives), the immediate community, or within the larger national culture. As a result, children adopted internationally into the United States are more likely to enter their families at older ages or with complex medical/developmental/social-emotional needs.

Although the vast majority of children adopted internationally enter the United States for purposes of adoption, there are a small, but growing, number of children who exit the United States for adoption into other countries. For example, in FY 2012, 99 children exited the United States for adoption by families in other countries (e.g., Canada, Netherlands, Ireland, United Kingdom). Little is known about the circumstances surrounding these adoptions and the eventual outcomes of the children who are adopted internationally from the United States.

In 2012, U.S. families adopted 8,868 children from other countries (compared with a peak of 22,884 in 2004). Children from China, Ethiopia, Russia, and South Korea represented 65% of children adopted internationally into the United States in 2012; 33% were from China alone. Although individual experiences vary, most children placed for international adoption have some history of poverty and social hardship in their home countries, and approximately 65% are adopted from orphanage/institutional settings. Many young infants are placed into orphanage care shortly after birth, while some older children have experienced family disruption resulting from parental illness, war, or natural disasters. Still others enter orphanage care following determination of significant abuse/neglect within their biologic families. The effects of institutionalization and other life stresses impact all areas of early growth and development. As a result, many children require specialized support and understanding to overcome the impact of stress and early adversity and to reach their full potential.

ROLE OF PEDIATRICIANS

Preadoption Medical Record Reviews

Adoption agencies are making increased efforts to obtain biological family health information and genetic histories to share with adoptive families prior to adoption. Pediatricians can help prospective adoptive parents understand the health and developmental history of a child and available background information from birth families in order to assess actual and potential medical risk factors to support adult decision making about the family’s ability to parent the waiting child. Under the Hague Convention on Protection of Children and Co-operation in Respect of Intercountry Adoption, agencies in the United States that arrange international adoptions must make efforts to obtain accurate and complete health histories on children awaiting adoption.

The nature and quality of medical and genetic information, when available, varies greatly. Poor translation and use of medical terminology and medications that are unfamiliar to U.S.-trained physicians are quite common. Results of specific diagnostic studies and laboratory tests performed outside of the United States should not be relied on and should be repeated once the child arrives in the United States. Paradoxically, review of the child’s medical records may raise more questions than provide answers. Each medical diagnosis should be considered carefully before being rejected or accepted. Country-specific growth curves should be avoided as they may be inaccurate or reflect a general level of poor health and nutrition in the country of origin. Instead, serial growth data should be plotted on U.S. standard growth curves; they may reveal a pattern of poor growth as a consequence of malnutrition or other chronic illness. Photographs or videotapes/DVDs may provide the only “objective” information from which medical status can be determined. Full-face photographs may reveal dysmorphic features consistent with fetal alcohol syndrome (see Chapter 106.2) or findings suggestive of other congenital disorders.

Preadoptive medical record reviews are also of potential value within the context of U.S. domestic adoptions. Biological family health information and genetic histories are often shared with adoptive families prior to adoption, and such information may become increasingly
relevant to the child as the child ages. The increase in “open” domestic adoptions, which encourages some degree of communication between participating biological and adoptive family members, may provide opportunities for long-term communication about medical and genetic conditions that might affect the adopted child.

In both international and domestic adoptions, frank interpretations of available information should be shared with the prospective adoptive parents. As noted by the American Academy of Pediatrics Committee on Early Childhood, Adoption and Dependent Care (1991), “It is not the pediatrician’s role to judge the advisability of a proposed adoption, but it is appropriate and necessary that the prospective parents and any involved agency be apprised clearly and honestly of any special health needs detected now or anticipated in the future.”

**Postadoption Medical Care**

**Arrival Visit—International Adoption**

All children with symptoms of an acute illness should receive immediate medical care after arriving in the United States. However, a significant number of children adopted internationally have acute or chronic medical problems that are not always immediately evident, including growth deficiencies, anemia, elevated blood lead, dental decay, strabismus, birth defects, developmental delay, feeding and sensory difficulty, and social-emotional concerns (see Chapter 215). After the child is settled in the new home, pediatricians should encourage adoptive parents to seek a comprehensive assessment of the child’s growth and development. The American Academy of Pediatrics recommends that all children who are adopted from other countries undergo routine screening for infectious diseases and disorders of growth, development, vision, and hearing (Tables 37-1 and 37-2). Additional tests (e.g., malaria) should be ordered depending on the prevalence of disease in the child’s country of origin (see Centers for Disease Control and Prevention’s interactive malaria map at [http://www.cdc.gov/malaria/map/](http://www.cdc.gov/malaria/map/)). If the child’s purified protein derivative test is negative, a repeat skin test should be performed in 4-6 mo; children may have false-negative tests because of poor nutrition. A positive purified protein derivative should be followed by a QuantiFERON-TB Gold test to determine if the response is the result of prior bacillus Calmette-Guérin vaccination (see Chapter 215). If they have not received hepatitis A vaccine prior to arriving in the United States, parents, other caregivers, and family members (siblings, grandparents, etc.) should also be immunized. In 1 survey, 65% of internationally adopted children had no written records of overseas immunizations; however, those with records appeared to have valid records, although doses were not necessarily acceptable according to the U.S. schedule (see Chapter 172). The diverse medical and developmental needs of internationally adopted children have led to the creation of specialty clinics throughout the United States, which may be a valuable resource for adoptive families at all stages in the adoption process.

**Developmental Delays**

At the time of adoption, many children exhibit delays in at least 1 area of development, but most exhibit significant gains within the first 12 mo after adoption. Those adopted before 6 mo of age usually demonstrate typical development, whereas those adopted at older ages have more variable outcomes. In the immediate postadoption period, it may be impossible to determine with any certainty whether a child’s developmental delays will be transient or long-lasting. Careful monitoring of development within the first year of adoption can identify a “developmental trend” over time that may be more predictive of long-term functioning than assessment at any specific point in time.

**Growth Delays**

Physical growth delays are common in both domestically and internationally adopted children, and may represent the combined result of many factors, for example, unknown/untreated medical conditions, malnutrition, and psychological deprivation. Weight and height at the time of adoption have been negatively correlated with the amount of time the child spent in adverse environments (i.e., orphanage care or in the care of highly neglectful biological families). Though most children experience a significant catch-up in physical growth following adoption, many remain shorter than their U.S. peers.

**Language Development**

For both domestic and international adoptees, genetic or biologic risk factors for poor language development may not have been identified preadoptively. Children adopted internationally typically have had little exposure to English, and it may not be possible to assess a child’s language abilities until they have had a chance to learn English. Most internationally adopted children of pre–school-age are able to attain English language skills equal to those born in the United States within 24 mo postadoption. In older children, delays in native language skills often predict delays in English acquisition. If language concerns persist following 1-2 yr in an enriching environment, assessment by a speech-language pathologist may be warranted.

**Table 37-2**

**Screening Tests for Infectious Diseases in International Adoptees**

<table>
<thead>
<tr>
<th>RECOMMENDED TESTS</th>
<th>OPTIONAL TESTS (FOR SPECIAL POPULATIONS OR CIRCUMSTANCES)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Hepatitis B virus serologic testing</em></td>
<td>GC/Chlamydia</td>
</tr>
<tr>
<td><em>Hepatitis B surface antigen (HBSAg)</em></td>
<td>Chagas disease serology</td>
</tr>
<tr>
<td><em>Antibody to hepatitis B surface antigen (anti-HBs)</em></td>
<td>Malaria thick and thin smears</td>
</tr>
<tr>
<td><em>Hepatitis C virus serologic testing</em></td>
<td>Urine for O&amp;P for schistosomiasis, if hematuria present</td>
</tr>
<tr>
<td><em>Varicella virus serologic testing</em></td>
<td></td>
</tr>
<tr>
<td><em>Syphilis serologic testing</em></td>
<td></td>
</tr>
<tr>
<td><em>Nonpreterm test (RPR, VDRL, or ART)</em></td>
<td></td>
</tr>
<tr>
<td><em>Treponemal test (MHA-TP or FTA-ABS)</em></td>
<td></td>
</tr>
<tr>
<td><em>Human immunodeficiency viruses 1 and 2 testing (ELISA if &gt;18 mo, PCR if &lt;18 mo)</em></td>
<td></td>
</tr>
<tr>
<td>Complete blood cell count with red blood cell indices and differential (if eosinophilia, see text)</td>
<td></td>
</tr>
<tr>
<td>Stool examination for ova and parasites (2-3 specimens)*</td>
<td></td>
</tr>
<tr>
<td>Stool examination for <em>Giardia lamblia</em> and <em>Cryptosporidium</em> antigen (1 specimen)*</td>
<td></td>
</tr>
<tr>
<td>Tuberculin skin test (with CXR if &gt;5 mm induration) or interferon-γ release assay*</td>
<td></td>
</tr>
</tbody>
</table>

*Repeat 3-6 mo after arrival.  
†See text.

**Table 37-1**

**Recommended Screening Tests for International Adoptees Upon U.S. Arrival**

**Screening tests**

- Complete blood cell count
- Hemoglobin identification
- Blood lead level
- Urinalysis
- Newborn screening (children <12 mo)
- Vision and hearing screening
- Developmental testing

Other screening tests to consider based on clinical findings and age of the child

- Detection of *Helicobacter pylori* antibody or 13C-urea breath test
- Stool cultures for bacterial pathogens
- Glucose-6-phosphate dehydrogenase deficiency screening
- Sickle cell
- Urine pregnancy test
- Infectious disease screening (see Table 37-2)

Eating Concerns
Initial concerns about eating, sleep regulation, and repetitive (e.g., self-stimulating or self-soothing) behaviors are common, especially among children adopted following a high degree of neglect or developmental trauma. Feeding concerns are sometimes linked to limited exposure to textured or solid foods during later infancy/toddlerhood. Children who have experienced chronic lack of food may not have developed an awareness of satiation cues, leading to hoarding or frequent vomiting. Feeding concerns often subside gradually with introduction of age-appropriate foods and parental support for positive feeding practices. Many children who were adopted following a significant period of malnutrition may eat an excessive amount of food. Unless the child is eating to the point of vomiting (which would indicate little awareness of satiation cues), it is generally best to allow them to eat until satiation. Typically within 6 mo, the child will regulate food intake appropriately. Occasionally, additional support from a speech pathologist or feeding specialist is warranted to address possible physical/psychological concerns that could impede proper feeding.

Sleep Concerns
Sleep is often disrupted as the child reacts to changes in routines and environments. Efforts to create continuity between the preadoption and postadoption environment can be helpful. Within the first 3-6 mo, as the child’s emotional self-regulation improves, many sleep concerns subside. Similarly, stereotypic behaviors, such as rocking or head banging, often diminish within the first few months following adoption.

Social and Emotional Development
Dyadic interactions between child and caretaker are a critical component to later regulatory functioning and social-emotional development. The amount and quality of individualized caretaking children have received prior to their adoption is usually unknown. In many instances, entry into a secure, stable home setting with consistent child-caring routines is sufficient to support the child’s emerging social-emotional development. At times, the child’s prior experiences or biologic disposition may result in behavior that is confusing to the adoptive parents. The child’s reactions may be subtle or difficult to interpret, interfering with the parents’ ability to respond in a sensitive manner. In these circumstances, additional support may be helpful to foster the emerging relationships and behavioral regulation in the newly formed family.

Racial Identity Development
An estimated 22% of adoptive families are interracial (where the racial background of the child differs from that of the parent/parents). In the vast majority of these adoptive placements, children of color have been adopted by white parents. Racial identity development, including ways to understand and respond to discrimination, is increasingly recognized as important in the overall development of children. Surveys of adults adopted transracially indicate that racial identity is of central importance at many ages, and tends to increase in significance during young adulthood. Integrating race/ethnicity into identity can be a complex process for all children, but it may be especially complicated when they are raised in a family where racial differences are noted. Adults raised within interracial families have noted the value of attending racially diverse schools and of having adult role models (e.g., teachers, doctors, coaches) who share their racial background. Parents who adopt transracially are often encouraged to support interactions within diverse communities and to discuss race (and associated discrimination) often within the family.

Toxic Stress
The cumulative amount of early adversity (e.g., numerous years within international orphanage care, extensive abuse/neglect prior to removal from biological family, or multiple foster care placements) experienced by a child prior to adoption, referred to as “toxic stress,” can impact both immediate placement stability and long-term functioning. The degree of presumed toxic stress may be helpful in interpreting a child’s behavior and supporting family functioning (see video at http://developingchild.harvard.edu/resources/multimedia/videos/three_core_concepts/toxic_stress/).

Family Support
There are unique aspects to adoptive family formation that can create familial stress and impact child and family functioning. Some adoptive families may have to address infertility, creation of a multiracial family, disclosure of adoptive status, concerns and questions the child may have about their biologic origins, and ongoing scrutiny by adoption agencies. In the case of gay/lesbian parents, there are often additional psychosocial stressors, including continued barriers to legal recognition of both parents in a gay/lesbian partnership that can negatively impact family functioning. Although most families acclimate well to adoption-related stressors, some parents experience post adoption depression and may benefit from additional support to ease the family’s transition.

Adoption Narrative
Families are encouraged to speak openly and repeatedly about adoption with their child, beginning in the toddler years and continuing through adolescence. Creating a “Lifebook” for the adopted child provides a way to support family communication about the child’s history and significant relationships (including birth family members) and to document the child’s important life transitions (e.g., through foster care or immigration to the United States). It is common, and normal, for children to have questions about adoption and their biological family throughout their development. An increase in cognitive understanding between ages 7 and 10 yr can sometimes increase adoption-related questions and/or distress. Youth who have questions about biological family members are increasingly able to access information via web-based searching, raising the importance of ongoing open communication about adoption. Pediatricians may need to respond to increased concerns/questions when the adoptee’s health and genetic history is incomplete or unknown. At any time, concerns about development, behavior, and social-emotional functioning may or may not be related to the child’s adoption history.

The vast majority of adopted children and families adjust well and lead healthy, productive lives. It is not common for adoptions to disrupt; disruption rates are higher among children adopted from foster care, which research associates with their age at time of adoption and/or a history of multiple placements prior to adoption. As a result of a greater understanding of the needs of families who adopt children from foster care, agencies are placing greater emphasis on the preparation of adoptive parents and ensuring the availability of a full range of postadoption services, including physical health, mental health, and developmental services for their adopted children.

Bibliography is available at Expert Consult.

37.1 Medical Evaluation of Immigrant (Foreign-Born) Children for Infectious Diseases

Stacene R. Maroushek

More than 210,000 foreign-born children (≤16 yr old) enter the United States each year as asylees, refugees, and immigrants including international adoptees. This number does not include undocumented children living and working in the United States, the U.S.-born children of foreign-born parents, or the approximately 2.7 million nonimmigrant visitors ≤16 yr old who legally enter the United States annually with temporary visas. With the exception of internationally adopted children, pediatric guidelines for screening these newly arrived children are sparse. The diverse countries of origin and patterns of infectious disease, the possibility of previous high-risk living circumstances (e.g., refugee camps, orphanages, foster care, rural/urban poor), the
Bibliography


limited availability of reliable healthcare in many economically developing countries, the generally unknown past medical histories, and interactions with parents who may have limited English proficiency, varied educational, or economic experiences, make the medical evaluation of immigrant children a challenging but important task.

Before admission into the United States, all immigrant children are required to have a medical examination performed by a physician designated by the U.S. Department of State in their country of origin. This examination is limited to completing legal requirements for screening for certain communicable diseases and examination for serious physical or mental defects that would prevent issuing a permanent residency visa. This evaluation is not a comprehensive assessment of the child's health and, except in limited circumstances, laboratory or radiographic screening for infectious diseases is not required for children <15 yr old. After entry into the United States, health screenings of refugees, but not other immigrants, are recommended to be done by the resettlement state. There is little tracking of refugees as they move to different cities or states. Thus, many foreign-born children have had minimal prearrival or postarrival screening for infectious diseases or other health issues.

Immunization requirements and records also vary depending on entry status. Internationally adopted children who are younger than 10 yr are exempt from Immigration and Nationality Act regulations pertaining to immunization of immigrants before arrival in the United States. Adoptive parents are required to sign a waiver indicating their intention to comply with U.S.-recommended immunizations, whereas older immigrants need only show evidence of up-to-date, not necessarily complete, immunizations before application for permanent resident (green card) status after arrival in the United States. Children exposed at ages 1-5 yr old. After entry into the United States, health screenings of refugees, but not other immigrants, are recommended to be done by the resettlement state. There is little tracking of refugees as they move to different cities or states. Thus, many foreign-born children have had minimal prearrival or postarrival screening for infectious diseases or other health issues.

Immunization requirements and records also vary depending on entry status. Internationally adopted children who are younger than 10 yr are exempt from Immigration and Nationality Act regulations pertaining to immunization of immigrants before arrival in the United States. Adoptive parents are required to sign a waiver indicating their intention to comply with U.S.-recommended immunizations, whereas older immigrants need only show evidence of up-to-date, not necessarily complete, immunizations before application for permanent resident (green card) status after arrival in the United States. Children may be asymptomatic; therefore, diagnoses must be made by screening tests in addition to history and physical examination. Because of inconsistent perinatal screening for hepatitis B and hepatitis C viruses, syphilis, and HIV, and the high prevalence of certain intestinal parasites and tuberculosis, all foreign-born children should be screened for these infections on arrival in the United States. Table 37-2 lists suggested screening tests for infectious diseases. In addition to these infections, other medical and developmental issues, including hearing, vision, dental, and mental health assessments; evaluation of growth and development; nutritional assessment; lead exposure risk; complete blood cell count with red blood cell indices; microscopic urinalysis; newborn screening (this could be done in nonneonates, too) and/or measurement of thyroid-stimulating hormone concentration; and examination for congenital anomalies (including fetal alcohol syndrome) should be considered as part of the initial evaluation of any immigrant child.

Children should be examined within 1 mo of arrival in the United States or earlier if there are immediate health concerns, but foreign-born parents may not access the healthcare system with their children unless prompted by illness, school vaccination, or other legal requirements. It is important to assess the completeness of previous medical screenings at any first visit with a foreign-born child.

Clinicians should be aware of potential diseases in high-risk immigrant children and their clinical manifestations. Some diseases, such as central nervous system cysticercosis, may have incubation periods as long as several years, and thus may not be detected during initial screening. On the basis of findings at the initial evaluation, consideration should be given to a repeat evaluation 6 mo after arrival. In most cases, the longer the interval from arrival to development of a clinical syndrome, the less likely the syndrome can be attributed to a pathogen acquired in the country of origin.

COMMONLY ENCOUNTERED INFECTIONS

Hepatitis B

See Chapter 350.

The prevalence of hepatitis B surface antigen (HBsAg) in internationally adoptees and refugee children ranges from 1-5% and 4-14%, respectively, depending on the country of origin, age, and year studied.

Prevalence of markers of past hepatitis B virus (HBV) infection is higher. HBV infection is most prevalent in immigrants from Asia, Africa, and some countries in Central and Eastern Europe, as well as the former Soviet Union (e.g., Bulgaria, Romania, Russia, and Ukraine), but also occurs in immigrants born in other countries. All immigrant children, even if previously vaccinated, coming from high-risk countries (HBsAg seropositivity >2%) should undergo serologic testing for HBV infection, including both HBsAg and antibody to HBsAg (anti-HBs), to identify current or chronic infection, past resolved infection, or evidence of previous immunization. Because HBV has a long incubation period (6 wk to 6 mo), the child may have become infected at or near the time of migration and initial testing might be falsely negative. Therefore, strong consideration should be given to a repeated evaluation 6 mo after arrival for all children, especially those from highly endemic countries. Chronic HBV infection is indicated by persistence of HBsAg for more than 6 mo. Children with HBsAg-positive test results should be evaluated to identify the presence of chronic HBV infection because chronic hepatitis B infection occurs in >90% of infants infected at birth or in the first year of life, and in 30% of children exposed at ages 1-5 yr. Once identified as being infected, additional testing to assess for biochemical evidence of severe or chronic liver disease or liver cancer should take place.

Hepatitis A

See Chapter 358.

Hepatitis C

See also Chapter 358.

The decision to screen children should depend on history (e.g., receipt of blood products; traditional percutaneous procedures such as tattooing, body piercing, circumcisions, or other exposures to reused, unsterile medical devices) and the prevalence of infection in the child's country of origin. Children from Eastern Mediterranean and Western Pacific countries, Africa, China, and Southeast Asia should be considered for hepatitis C infection screening. All children coming from Egypt, which has the highest known seroprevalence (12% nationally and 40% in some villages), should be tested for hepatitis C.

Intestinal Pathogens

Fecal examinations for ova and parasites by an experienced laboratory will identify a pathogen in 15-35% of internationally adopted children; prevalence rates in immigrants and refugees range from 8-86%. The prevalence of intestinal parasites varies by country of origin, time period when studied, previous living conditions (including water quality, sanitation, and access to footwear) and the age of the child, with toddler/young school-age children being most affected. If documented predeparture treatment was given, an eosinophil count should be performed. An absolute eosinophil count of >400 cells/μL, if persistently elevated for 3-6 mo after arrival, should prompt further investigation for tissue-invasive parasites such as Strongyloides (see Chapter 295) and Schistosoma (see Chapter 300) species. If no documented predeparture treatment was given, 2 stool ova and parasite specimens obtained from separate morning stools should be examined by the concentration method, and an eosinophil count should be performed. If the child is symptomatic, including evidence of poor physical growth, but no eosinophilia is present, a single stool specimen should also be sent for Giardia lamblia (see Chapter 282) and Cryptosporidium parvum (see Chapter 283) antigen detection. All potentially pathogenic parasites found should be treated appropriately. All nonpregnant refugees >2 yr of age coming from sub-Saharan Africa and Southeast Asia should be presumptively treated with predeparture albendazole.

Tuberculosis

See also Chapter 215.

Tuberculosis (TB) commonly is encountered in immigrants from all countries because Mycobacterium tuberculosis infects approximately 30% of the world's population. Latent TB infection rates range from 0.6-30% in adoptees and up to 60% in some refugee children from North Africa and the Middle East. Prior to 2007, chest radiographs or
tuberculin skin tests were generally not administered in children <15 yr of age and reports indicate that 1-2% of these unscreened children may enter the United States with undiagnosed active TB disease.

Since 2007, TB Technical Instructions for Medical Evaluation of Aliens have required that children ages 2-14 yr undergo a TB skin test if they are medically screened in countries where the TB rate is 20 cases or more per 100,000 population. If the skin test is positive, a chest x-ray is required. If the chest x-ray suggests TB, cultures and 3 sputum smears are required, all before arrival in the United States. This requirement is being phased in over a number of years, and some countries with a case rate of 20 per 100,000 may not currently be screening children. Check with the Centers for Disease Control and Prevention, Division of Global Migration and Quarantine for latest information (www.cdc.gov/ncidod/dq/technica.htm).

**Congenital Syphilis**
See Chapter 218.

**HIV Infection**
See Chapter 276.

**Immunizations**
See Chapter 172.

*Immigrant children and adolescents should receive immunizations according to the recommended schedules in the United States for healthy children and adolescents.* Some immigrants will have written documentation of immunizations received in their birth or home country. Although immunizations such as bacillus Calmette-Guérin, diphtheria and tetanus toxoids, and pertussis (DTP), poliovirus, measles, and hepatitis B virus vaccines often are documented, other immunizations, such as *Haemophilus influenzae* type b, mumps, and rubella vaccines, are given less frequently, and *Streptococcus pneumoniae*, human papillomavirus, meningococcal, and varicella vaccines are given rarely. When doubt exists, an equally acceptable alternative is to reimmunize the child. Because the rate of more serious local reactions after diphtheria, tetanus toxoid, and acellular pertussis vaccine increases with the number of doses administered, serologic testing for antibody to tetanus and diphtheria toxins before reimmunizing, or if a serious reaction occurs, can decrease risk.

In children older than 6 mo with or without written documentation of immunization, testing for antibodies to diphtheria and tetanus toxoid and poliovirus may be considered to determine whether the child has protective antibody concentrations. If the child has protective concentrations, then the immunization series should be completed as appropriate for that child’s age. In children older than 12 mo, measles, mumps, rubella, and varicella antibody concentrations may be measured to determine whether the child is immune; these antibody tests should not be performed in children younger than 12 mo because of the potential presence of maternal antibody.

*Bibliography is available at Expert Consult.*
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The placement of children in out-of-home care has served the needs of children in many societies worldwide throughout history. The institution of foster care was developed in the United States as a temporary resource for children during times of family crisis and is rooted in the principle that children fare best when raised in family settings.

The 1989 United Nations Convention on the Rights of the Child, a legally binding international instrument, addresses the need for such care for all children worldwide. Regardless of its setting, the mission of foster care is to provide for the safety, permanency, and well-being of children while assisting their families with services to promote reunification.

**Epidemiology**

The number of children in foster care worldwide is unknown, although it has been estimated that 8 million may be in foster and residential care. On September 11, 2011, approximately 400,540 children in the United States resided in foster care, representing a downward trend since 1999, when the daily average of children in care was 567,000. This decrease has occurred despite an increase in maltreatment reports, as child welfare offers families more preventive services and placement with relatives or nonrelative caregivers (kinship care) as an alternative to removal, resulting in fewer admissions. Reunification rates and adoption of children from foster care have also increased. Court ordered and informal kinship care have increased, accounting for up to 7% of children.

Approximately 33% of children in foster care in the United States are younger than the age of 5 yr and 35% are older than age 12 yr. The largest subset is white (41%) with significant percentages of black (27%) and Hispanic (21%) children. The average length of stay has dropped to a mean of 23.9 mo (median: 13.5 mo), although 31% of children remain in foster care for more than 2 yr. Only approximately 52% of children achieve reunification. Approximately 8% go to relatives, while approximately 20% (50,000 children) are adopted out of foster care annually. Among remaining children, 11% emancipate, 6% enter into long-term state guardianship, 1% run away, and 2% transfer to other institutions. In 2011, there were 343 deaths in foster care.

Most children live in nonrelative foster (47%) or certified relative foster (27%) family care, and 4% reside in a preadoptive home, although this is less than 20% of the children who are awaiting adoption. Approximately 15%, mostly adolescents, live in group homes or residential settings. The average number of placements a child experiences in foster care is not included in Adoption and Foster Care Reporting System, but important predictors include severe behavioral and/or developmental problems, larger sibling group size, and longer time spent in foster care. Within 12 months, nearly all emancipated youth have at least one homeless night and, within a decade, less than half have a high school degree and most are living in poverty and have high rates of posttraumatic stress disorder and depression.

**Legislation in the United States**

In the United States, the Adoption and Safe Families Act (P.L. 105-89), passed in 1997, requires that a permanency plan be made for each child no later than 12 months after entry into foster care and that a petition to terminate parental rights typically be filed when a child has been in foster care for at least 15 of the previous 22 months. The Fostering Connections and Promoting Adoptions Act of 2009 (P.L. 110-351) focused on incentives for guardianship and adoption, supports for the young adults at the age of emancipation, and rights of Native American children to care within their tribe. This latter act also contained a clause requiring states to develop and coordinate health care systems for children in foster care in collaboration with Medicaid and pediatricians.

**Early Childhood Trauma Leads to Poor Health Outcomes**

Children in foster care have high rates of early childhood trauma and adversity. More than 70% have a history of abuse, neglect, or both. More than 80% have experienced significant domestic and/or community violence. Birth parents have high rates of mental illness, criminal justice system involvement, substance abuse, unemployment, and cognitive impairment. Many children have had prenatal substance exposure, multiple caregivers of varying quality, and are from families with long involvement with child protective services.
Removal from the family of origin may compound trauma although some children experience relief at removal from a chaotic, abusive, or dangerous home. Most children miss their family, worry about their parents and siblings, and long for reunification. Separation, loss and grief, unpredictable contact with birth parents, placement changes, the process of terminating parental rights, and the sheer uncertainty of foster care may further erode a child’s well-being.

Childhood trauma is correlated with poor developmental, behavioral and health outcomes. Early trauma and chronic stress adversely affect the neurobiology of the developing brain, especially those areas involved in attention, emotional regulation, memory, executive function, and cognition. As a result, shortened attention span, hyperactivity, poorer cognitive function, aggression, and memory issues are problems encountered frequently encountered among children in foster care.

**HEALTH ISSUES**

Multiple childhood adversities and the receipt of fragmented and inadequate health services before placement into foster care mean that children enter foster care with a high prevalence of chronic medical, mental health, developmental, dental, and educational problems (Table 38-1), and so are defined as children with special healthcare needs. The greatest single healthcare need of this population is for high-quality, evidence-based mental health services to address the impacts of prior and ongoing trauma, loss, and unpredictability. In addition, they have higher rates of asthma, growth failure, obesity, vertically transmitted infections, and neurologic conditions than the general pediatric population. Adolescents need access to reproductive health and substance abuse services. Up to 60% of children <5 yr have a developmental delay in at least 1 domain and more than 40% of school-age children qualify for special education services. Unfortunately, educational difficulties persist despite improvements in school attendance and performance after placement in foster care.

Although children in foster care are children with special healthcare needs, often they lack access to the services they need. Most public and private child welfare agencies do not have formal arrangements for accessing the needed array of health services and rely on local physicians and/or health clinics funded by Medicaid. Health histories are often sparse at admission because many have lacked regular care or their biological parents may not be available or forthcoming. Once children enter foster care, there is often a diffusion of responsibility across caregivers and child welfare. Foster parents usually receive little information about a child's healthcare needs, but they are typically expected to decide when and where children receive healthcare services. Child welfare case workers are responsible for ensuring that a child’s health needs are addressed but coordination across multiple healthcare providers may be daunting. Uncertainty about who is legally responsible for making healthcare treatment decisions and who may have access to health information may delay or result in the denial of healthcare services.

**Table 38-1 | Health Issues of Children in Foster Care**

<table>
<thead>
<tr>
<th>CHRONIC MEDICAL PROBLEMS</th>
<th>Affect 40-60% of children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma, dermatologic, neurologic, obesity, growth failure, hearing, and vision problems are most common</td>
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<table>
<thead>
<tr>
<th>ABUSE AND NEGLECT</th>
<th>&gt;70% of children have a history of abuse and neglect at entry into foster care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitor at all health visits for abuse or neglect</td>
<td></td>
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<table>
<thead>
<tr>
<th>COMPLEX CHRONIC MEDICAL PROBLEMS</th>
<th>Involves 10% of children in foster care</th>
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</thead>
<tbody>
<tr>
<td>Children may be dependent on medical technologies or have multiple disabilities</td>
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<table>
<thead>
<tr>
<th>MENTAL HEALTH CONCERNS</th>
<th>Affects 80% of children &gt;4 yr of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result of childhood trauma and adversity</td>
<td></td>
</tr>
<tr>
<td>Most common diagnoses are adjustment disorder, posttraumatic stress disorder, attention-deficit/hyperactivity disorder, oppositional defiant disorder, and conduct disorder</td>
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</tr>
<tr>
<td>Externalizing problems are more likely to result in therapy</td>
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<table>
<thead>
<tr>
<th>DEVELOPMENTAL PROBLEMS</th>
<th>60% of children &lt;5 yr of age have at least 1 documented delay</th>
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<tbody>
<tr>
<td>Commonly affect communication, cognition, problem-solving, and personal-social domains</td>
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<table>
<thead>
<tr>
<th>DENTAL PROBLEMS</th>
<th>35% of children have significant dental disease</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>ADOLESCENT HEALTH ISSUES</th>
<th>High rates of sexually transmitted infections, high-risk behaviors, and substance abuse</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>EDUCATIONAL PROBLEMS</th>
<th>Half of special education placements relate to behavioral or emotional issues, not cognitive</th>
</tr>
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<tbody>
<tr>
<td>Only 32% of adolescents eventually graduate from high school; 32% obtain a General Equivalency Diploma</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>FAMILY RELATIONSHIP PROBLEMS</th>
<th>100% of children have family relationship problems</th>
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</table>

The American Academy of Pediatrics (AAP) and Child Welfare League of America published updated general guidelines for the healthcare of this special needs population in 2007. The AAP has published detailed healthcare standards for children in foster care, available on the Healthy Foster Care America website. Children should receive healthcare services in a medical home setting where they receive comprehensive healthcare that is continuous over time (Table 38-2). Compassionate, culturally competent healthcare that is trauma-informed means that health staff should understand the effects of past trauma and ongoing uncertainty and loss on a child’s health and well-being, and that of their birth and foster families. Children should be seen early and often when they first enter foster care to identify all their health issues, and to support the child and foster parent through a major transition that involves considerable loss and adjustment for the child and many challenges for the foster parent.

The AAP recommends that every child in foster care have comprehensive medical, dental, developmental, and mental health assessments within 30 days of entering foster care. Almost every child in foster care deserves a full mental health evaluation to assess for the impact of trauma and loss on emotional well-being. Psychotropic medication should only be considered, if at all, after a thorough high-quality mental health evaluation by a pediatric-trained mental health professional. It is wise for the pediatrician to remember that inattention, impulsivity and hyperactivity may reflect the impact of past trauma on the developing brain rather than attention-deficit/hyperactivity disorder (see Chapter 33). Childhood trauma impairs cognition and memory (see Chapter 40) so that children <6 yr of age should receive a comprehensive developmental assessment, while older children should receive a comprehensive educational assessment. The caseworker should provide consents for healthcare and any available health history, and encourage the appropriate involvement of the birth parent. The primary care provider should help caseworkers and foster parents obtain and interpret the results of these assessments. Pediatricians, caregivers, and caseworkers should share health information.

Foster parents are the major therapeutic intervention of the foster care system, and pediatricians should provide them with appropriate education and support. Important topics include positive parenting strategies, supporting children through transitions, providing a consistent and nurturing environment, and helping children heal from past trauma and adversity (Table 38-3). Foster and birth parents may need extensive education about behavioral and emotional problems within the context of the child’s trauma history to remove blame and promote healing. Minimizing conflict among caregivers is extremely important as a child ideally has affection and loyalty for all of the child’s caregivers. Pediatricians should focus on both caregiver (foster and birth...
Table 38-2  Pediatric Medical Home for Children in Foster Care

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>APPLICATION IN FOSTER CARE</th>
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| Comprehensive healthcare | Perform comprehensive admission assessment within 30 days of entry  
Ensure access to mental health, developmental, and dental evaluation and services  
Screen and refer as needed for abuse and neglect |
| Coordination of care | Make timely referrals and follow up subspecialist visits  
Communicate with caseworkers, foster parents, and legal professionals  
Maintain a comprehensive medical record despite changes in placement |
| Compassionate care | Understand and educate children, families, and other healthcare professionals on the impact of early childhood adversities, trauma and ongoing uncertainties of foster care on the developing child  
Promote positive purposeful parenting strategies and minimizing conflict among caregivers |
| Child-centered and family-focused care | Prioritize the needs of children first and foremost  
Partner with families to increase understanding of a child’s needs  
Focus on the strengths of children and families |
| Continuity of care | Invite children to remain patients throughout their stay in foster care, and beyond when feasible |
| Cultural competence | Extend this concept to include the microculture of foster care and the multiple transitions that can further erode a child’s well-being. Understand the roles of caseworkers, foster parents, law guardians, etc. |
| Accessibility | Create a welcoming environment for children and all of their families (birth, foster, kin, preadoptive) |

Table 38-3  Anticipatory Guidance for Children in Foster Care

<table>
<thead>
<tr>
<th>SITUATION</th>
<th>ANTICIPATORY GUIDANCE FOR FOSTER PARENTS</th>
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| Preparing for visits | Educate foster/kinship parents about impact of visitation on children  
Send familiar object with child to visit  
Have child draw picture to give birth parent  
Reassure child that foster parent will be there when child returns from visits  
Advise all caregivers to minimize conflict with and negativity toward each other |
| Returning from visits and other transitions | Greet child warmly and help with unpacking  
Establish reentry rituals, such as quiet play, reading together, having a healthy snack |
| Relationship with birth parent(s) | Encourage caseworker to have birth parents keep child’s rituals and routines consistent with those in foster home (vice versa when appropriate)  
Focus on birth parent’s positive qualities; maintain a neutral affect |
| Building on child’s strengths | Encourage participation in child-directed play.  
Encourage participation in normalizing activities (such as hobbies or sports)  
“Catch the child being good”  
Encourage specific praise  
Provide child with words for emotions  
Ignore negative behavior unless there is a safety issue |
| Preparing for court dates | Foster/kinship parent, caseworker or law guardian should explain purpose of court hearings to child in simple terms |
| School | If changing schools, visit school together a few times, and meet the teacher  
Check in regularly (weekly or monthly depending on need) with child’s teacher |
| Adolescent | Decide what issues demand firm limits and guidelines (curfews, no smoking, party at a friend’s house, etc.), what issues are not important and can be left up to teen (hair length and color, etc.) and what issues are ideal for negotiation (transportation to a school function, style of dress etc.)  
Encourage responsible decision-making by recognizing and complimenting it.  
Encourage after-school activities.  
Teach driving when age and developmentally appropriate  
Encourage teen to seek employment and teach job skills  
Help teen to identify mentors and focus on the future |

parent) and child strengths. For teens and young adults in foster care, the pediatrician should provide anticipatory guidance around education, identity formation in the face of past trauma, independent decision making, health promotion, and developing the skills and competencies needed for a successful future life. The pediatrician should advocate for placement stability in a nurturing and responsive foster family where caregivers possess the appropriate skills to help children and youth heal.

Bibliography is available at Expert Consult.
Bibliography
AAP District II Task Force on Health Care for Children in Foster Care, District II Committee on Early Childhood, Adoption, and Dependent Care: *Fostering health: health care for children and adolescents in foster care*, Elk Grove, Ill, 2005, AAP. Available through the American Academy of Pediatrics Bookstore. Now available through the Healthy Foster Care America website under Tools and Resources at: www.aap.org/fostercare.


The reach of violence, whether as the victim, perpetrator, or witness, whether in person or through the media, is far, deep, and long-standing across the globe (see Chapter 1). Exposure to violence disrupts the healthy development of children in a myriad of ways. Pediatric clinicians must be competent to address these issues in impacted children and families under their care and also have a wider responsibility to advocate on local, state, national, and international levels for safer environments in which all children can grow and thrive.

Witnessing violence is detrimental to children. Because their scars as bystanders are emotional and not physical, the pediatric clinician may not fully appreciate their distress and thereby miss an opportunity to provide needed interventions. For children not living in war zones, the source of first exposure to violence is often intimate partner violence. According to data from the National Center for Posttraumatic Stress Disorder (PTSD), 20–30% of American women will be physically abused by a partner at least once in their lifetimes. Similarly in the 2010 National Intimate Partner and Sexual Violence Survey administered by the Centers for Disease Control and Prevention (CDC), 1 in 4 women and 1 in 7 men have been the victim of severe physical violence by an intimate partner, affecting more than 12 million people each year. Slightly more than half of female victims of intimate partner violence live in households with children <12 yr of age; family violence is most likely to be perpetrated by those between the ages of 18 and 30 yr and most victims are impacting before 24 yr of age. Across studies, 7–23% of youths in general population surveys experienced exposure to intimate partner violence, 36–39% of youth in intimate partner violence cases have witnessed the violence, and 45–46% of primary caregivers in child maltreatment investigations have experienced intimate partner violence. In a national survey, 50% of the men who frequently assaulted their wives also frequently abused their children. Most of the children were injured when they intervened to protect their mother from her partner (see Chapter 40). Children who witness domestic violence are at higher risk for negative medical outcomes including increased risk of obesity, asthma, and PTSD. In addition, these children are at higher risk for other traumatic events; for example, in a sample of 120 preschool children (age 4–6 yr) exposed to intimate partner violence in the past 2 yr, 38% were exposed to additional traumatic events, including sexual assaults by family members, physical assaults, serious accidents, and/or life-threatening illnesses.

Another source of witnessed violence is community violence. Community violence in the United States is a serious problem that disproportionately affects children from low-income areas. According to the 2011 National Survey of Children’s Exposure to Violence, approximately 22% of children had witnessed violence in their family or in their community in the year prior to the survey, and of all the horrors the survey inquired about—assaults and bullying, sexual victimization, maltreatment by a caregiver, and theft or vandalism—nearly 60% of children had experienced or witnessed one of them. Young children living in high crime and violence areas observe death more frequently and at younger ages than do children growing up in more secure surroundings. Witnessing acts of violence may be a significant stressor in children’s lives. If children’s coping skills are not sufficient to deal with violent situations, stress may be manifested as psychological, physical, or behavioral symptoms.

The most ubiquitous source of witnessing violence for children in the United States is media violence. The average child 2–5 yr of age watches 20–30 hr of television a week, hours that are increasingly filled with scenes of violence, not only on commercial television but also on news outlets. In addition, the wider array of “screen time” children are exposed to, including computer, smart phones, and video games, increases the opportunities for violent events to enter the lives of children. In particular, recent tragic events, including mass shootings and acts of terrorism, have increased the specter of fear among children. Although exposure to media violence cannot be equated to exposure to real-life violence, many studies confirm that media violence desensitizes children to the meaning and impact of violent behavior. Not all children are equally affected by media violence. Children most at risk from viewing violence may be children who are also exposed regularly to real-life violence in their homes and communities. Table 39–1 lists interventions to reduce exposure to media violence.

IMPACTS OF VIOLENCE

The violence children experience and witness also has a profound impact on health and development. In a cross-sectional analysis of a Head Start preschool-age cohort, being abused, exposure to domestic violence, and having a mother using substances were associated with a higher number of health problems. Beyond injuries, violence affects children psychologically and behaviorally; it may influence how they view the world and their place in it. Children can come to see the world as a dangerous and unpredictable place. This fear may thwart their exploration of the environment, which is essential to learning in childhood. Children may experience overwhelming terror, helplessness, and fear even if they are not immediately in danger. Preschoolers are most vulnerable to threats that involve the safety (or perceived safety) of their caretakers. High exposure to violence in older children correlates...
with poorer performances in school, symptoms of anxiety and depression, and lower self-esteem. Violence, particularly domestic violence, can also teach children especially powerful early lessons about the role of violence in relationships. Violence may change the way that children view their future; they may believe that they could die at an early age and thus take more risks, such as drinking alcohol, abusing drugs, not wearing a seatbelt, and not taking prescribed medication.

Some children exposed to severe and/or chronic violence may suffer from PTSD, exhibiting constricted emotions, difficulty concentrating, autonomic disturbances, and reenactment of the trauma through play or action (see Chapters 1 and 25). Although young children may not fully meet these criteria, certain behavioral changes are commonly associated with exposure to trauma, such as sleep disturbances, aggressive behavior, new fears, and increased anxiety about separations (“clinginess”). A particular challenge in treating and diagnosing pediatric PTSD is that a child’s caregiver exposed to the same trauma may be suffering from it as well.

Diagnosis and Follow-up

The simplest way to recognize whether violence has become a problem in a family is to screen both the parents and the children (after ≈8 yr of age) on a regular basis. This practice is particularly important during pregnancy and the immediate postpartum period when women may be at highest risk for being abused. It is important to assure families that they are not being singled out, but that all families are asked about their exposure to violence. A direct approach may be useful: “Violence is a major problem in our world today and one that impacts everyone in our society. Thus I have started asking all my patients and families about violence that they are experiencing in their lives. …” In other cases, beginning with general questions and then moving to the specific may be helpful. “Do you feel safe in your home and neighborhood? Has anyone ever hurt you or your child?” When violence has impacted the child, it is important to gather details about symptoms and behaviors.

The pediatrician can effectively counsel many parents and children who have been exposed to violence. Regardless of the type of violence to which the child has been exposed, the following components are part of the guidance: careful review of the facts and details of the event, gaining access to support services, providing information about the symptoms and behaviors common in children exposed to violence, assistance in restoring a sense of stability to the family in order to enhance the child’s feelings of safety, and helping parents talk to their children about the event. When the symptoms are chronic (>6 mo in duration) or not improving, if the violent event involved the death or departure of a parent, if the caregivers are unable to empathize with the child, or if the ongoing safety of the child is a concern, it is important that the family be referred to mental health professionals for additional treatment.

Bibliography is available at Expert Consult.

39.1 Bullying, Cyberbullying, and School Violence

Douglas Vanderbilt and Marilyn C. Augustyn

BULLYING ("TRADITIONAL BULLYING")

Bullying is the assertion of power through social, emotional, or physical means of aggression that involves a bully repeatedly and intentionally targeting a weaker victim. Bullying affects a large number of children and lays the groundwork for long-term depression, suicidality, psychotic symptoms, conduct problems, and psychosomatic concerns seen in children. Children can move between being a bully, victim, bully-victim (both a bully and a victim at different times), or bystander. Bullying can be direct, involving physical aggression such as hitting, stealing, and threatening with a weapon or verbal aggression such as name-calling, public humiliation, and intimidation, or it can be indirect, involving relational aggression such as spreading rumors, social rejection, exclusion from peer groups, and ignoring. Bullying occurs most frequently at school when there is minimal supervision during breaks, recess, and lunch at playgrounds, in hallways, and en route to and from school.

CYBERBULLYING

Cyberbullying is an emerging form of bullying that takes place using electronic technology (text messaging, mass emailing, Internet chat rooms, social networking sites, etc.). In contrast to traditional bullying, it allows complete anonymity to the bully and has enormous capacity for “reach.” Given its recent recognition and ongoing evolution, much remains unknown about its causes and therefore prevention strategies; what is clear is that the psychological consequences can be devastating for the victim. Victims of cyberbullying may be at higher risk for suicide (see Chapter 27) than victims of traditional bullying.

Epidemiology

Bullying is a common occurrence for schoolchildren. Bullying occurs in all countries, affecting anywhere from 9-54% of youth. Apparent rates of bullying are influenced by the manner in which questions are asked; youth are more willing to acknowledge having engaged in activities which can be categorized as forms of “bullying” than they are to respond to a question asking them if they have acted in a bullying manner or have been a bully.

The 2011 Indicators of School Crime and Safety reported that 28% of youth (31% females and 25% males) ages 12 to 18 yr had been bullied at school, 18% were ridiculed, 18% were the subject of rumors, 9% were cyberbullied, 8% were purposefully pushed, shoved, or tripped (leading to injury in about 1/5), 6% were purposefully excluded from activities, 5% were threatened with harm, and 3% had personal property that had been purposefully destroyed.

With regard to traditional bullying, the 2009 Youth Health Risk Behavior Survey (YHRBS), concurred that males and females were equally likely to report having been bullied (victims); males were 2.5 times more likely than females to report having bullied others. Rates of bullying or being bullied did not differ by race/ethnicity, except that Hispanics were less likely to report having bullied someone. Other surveys have found that students who carry weapons, smoke, and drink alcohol more than 5-6 days/wk were at greatest risk for moderate bullying. Those who carry weapons, smoke, have more than 1 alcoholic drink per day, have above-average academic performance, moderate/high family affluence, and feel irritable or bad-tempered daily were at greatest risk for frequent bullying. Negative parenting behavior is related to a moderate increase of risk for becoming a bully/victim and small to moderate effects on victim status at school.

Rates of cyberbullying victimization have ranged from 4-72% and of cyberbullying from 3-23%, in part reflecting variations in definitions and sampling design. According to the 2009 YHRBS, males and females were equally likely to experience cyberbullying, but males were >3-fold likely to report having been a cyberbully. Rates of cyberbullying (as victim or perpetrator) did not differ by race/ethnicity. Seniors were more likely to be involved in cyberbullying than youth in other grades.

A separate study conducted among 918 students in grades 6 through 12, found considerable overlap between traditional and cyberbullying/victimization; three-fourths were not involved as victim or bully in either traditional or cyberbullying. Most victims of traditional bullying were not involved in cyberbullying, but those with involvement were more likely to be victims. Most traditional bullies were not involved in cyberbullying but those who were, were generally bullies.

Health Outcomes

Involvement in bullying is associated with poorer psychosocial adjustment; bullies, victims, and bully-victims report greater health problems and poorer emotional and social adjustment. Victims tend to be either physically weak and emotionally vulnerable or provocative, with attention or conduct problems and have lower social status and higher social marginalization and isolation. Overall, both victim and
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**Bibliography**


**Websites**


bull-victims have been described as anxious, insecure, lonely, and lacking social skills. They may have learning disabilities, autism spectrum disorder, or poor physical skills. They have more depression, psychosomatic complaints, medication use, and suicidality. Chronic or severe victimization in childhood has been shown to be associated with psychotic symptoms in early adolescence. Long-term consequences in adulthood of being bullied as a child include depression, poor self-esteem, and abusive relationships. In the 2009 YHRRBS, traditional bullying victimization was a significant predictor of depression for males and females and a direct contributor to suicidal behavior for females.

Bullies have higher rates of both conduct disorders and social standing. They have the lowest rates of adjustment problems because of their higher social status. They make friends that support their bullying behavior but other peers avoid them. Bullies who acknowledge their behavior have higher rates of depression and psychologic distress compared to those who deny their bullying behavior. In the 2009 YHRRBS data, traditional bullying predicted depression in females but not in males. Depression significantly mediated the relationship between bullying and suicidal behavior among both genders. They have higher negative attitudes toward school and use more tobacco, alcohol, and other drugs. Childhood bullies have a 4-fold increase in criminal behavior by their mid-20s and are at higher risk of dropping out of school. They have lower likelihood of being employed and having stable long-term romantic relationships. The bully-victim has problems with peer relationships and high rates of depression, loneliness, alcohol use, and weapon carrying.

Less is known about the characteristics of cyber bullies or victims and their long-term consequences. In the 2009 YHRRBS data, cyber victimization was associated with depression in women but not men, and contributed to suicidal behavior among women. Cyberbullying was not associated with depression among men or women. Lower academic achievement and lower self-esteem are associated with cyberbullying perpetration and victimization, and anxiety symptoms with cyberbullying perpetration.

**SCHOOL VIOLENCE Epidemiology**

School violence is a common but nonnormative aspect of development occurring throughout the world. Almost 40% of U.S. schools report a least 1 violent incident to police, with more than 600,000 victims of violent crime per year. Among 9th to 12th graders, 8% were threatened or injured on school property in the last 12 mos, and 14% were involved in a physical fight over the last year. School-associated violent deaths are rare. Seventeen homicides of children ages 5–18 yr occurred at school during the 2009–2010 school year. Of all youth homicides, less than 2% occur at school. These are more likely to occur at the beginning of each semester with perpetrators previously giving warning signals. Whereas urban schools experience more episodes of violence, the episodes of rare "rampage" gun violence in rural and suburban schools demonstrate that no region is immune to lethal violence.

**Risk Factors**

Bullying and weapon carrying may be important precursors to more serious school violence. Among perpetrators of violent deaths at school, 20% had been bullying victims, and 6% of all students carried a weapon to school in the last 30 days. Nonlethal violence, mental health problems, racial tensions, student attacks on teachers, and the effects of rapid economic change in communities can all lead to school violence. Individual risk factors for violence include prior history of violence, drug, alcohol, or tobacco use, association with delinquent peers, poor family functioning, poor grades in school, and poverty in the community.

Family risk factors include early childbearing, low parental attachment and involvement, authoritarian or permissive parenting styles, and poverty. There is more school violence in areas with higher crime rates and more street gangs, with little improvement with additional security measures. These risks take away students' ability to learn in a safe environment and leave many children with traumatic stress and grief reactions. Behavioral genetics and developmental psychology are beginning to elucidate the bidirectional gene-environment interactions that promote these endemic episodes of violence.

**TREATMENT AND PREVENTION OF BULLYING AND SCHOOL VIOLENCE**

Pediatric providers are in a unique position to screen, treat, and advocate for reducing the impact of school violence by assisting those affected and seeking to prevent further occurrences. Signs of a child being bullied include physical complaints such as insomnia, stomachaches, headaches, and new-onset enuresis (see Chapter 23.3). *Psychologic symptoms*, such as depression (see Chapter 26), loneliness, anxiety (see Chapter 25), and suicidal ideation, may occur. Behavioral changes, such as irritability, poor concentration, school avoidance, and substance abuse, are common. *School problems*, such as academic failure, social problems, and lack of friends, can also occur. Additional vigilance must be made for those children with chronic medical illnesses, obesity, physical deformities, and learning disabilities or autism spectrum disorder who may be potential targets. A bully may be more difficult to identify because of the bully's desire to obscure the behavior. Children who are aggressive, overly confident, lacking in empathy, and having conduct problems may need careful screening. The physical, behavioral, psychologic, and school symptoms of bullying may overlap with other conditions such as medical illness, learning problems, and psychologic disorders.

Simple questions to ask children include **Borris**: Have you been bullied or bullied anyone? Have you observed bullying going on? How did you respond? Do you feel like you are repetitively singled out as a bully or a victim? Have you sent or receiving things over the Internet that you think may represent bullying? Do you feel stuck in bullying situations? And for parents **Wart**: Have you witnessed or heard about your child being picked on or picking on other kids? Have there been any recent changes about your child's *attitude*, attention and concentration changes? What are your community *rules* about bullying? Has your child *talked* to you about being picked on or witnessing other kids being picked on?

**Management** of bullying and school violence involves systemic interventions with parents, victims, bullies, and the school. Interventions should include supporting families, victims, and bullies; identifying and referring those children in need of further academic and mental health services; and expecting behavioral change from the bully and social change from the school environment. The clinician should listen empathetically to the child to help empower and reassure the child. The clinician should not blame the victim or trivialize the child's concern. Suggestions should include having the child seek social support from teachers and friends and avoiding situations where the bullying may occur. Role-playing an encounter can be helpful for the child. Extracurricular activities, like drama clubs, mentoring programs, and sports, can be used to help to bolster the child's self-esteem. The clinician should identify safety issues, such as suicidal ideation and plans, substance abuse, and other high-risk behaviors.

Once a bully is identified and appropriate screening for family risk factors is completed, the clinician should educate the parents and child about the seriousness of the behavior and its potential consequences. The clinician should label the behavior as the problem and help the family and child to acknowledge the behavior as hurtful. For example: “Do you feel bad when other children hurt your feelings?” “Bullying hurts other children's feelings.” The school and parents should ensure accountability for the child's subsequent behavior. Parental mental health and resource risk factors should also be addressed.

Beyond individual- and family-based interactions, providers also can advocate for systemic interventions through school-community violence and bullying prevention programs. Targeted school curricula or social skills group interventions have not been found to reduce bullying in several well-done studies. Successful interventions involve whole school approaches that involve multiple disciplines. These broad-based programs simultaneously include school-wide rules and...
sanctions, teacher training, classroom curriculum, conflict resolution training, and individual counseling. Mentoring programs and an increased number of social workers can also be helpful in reducing bullying. Addressing access to firearms, involving community organizations and parents, enhancing the built environment of schools and community, and supporting youth self-esteem are important in creating a safe school climate. Targeting larger societal risk promoters of violence in the neighborhood and school culture are also avenues for improving school violence. In Denmark, an intensive national-level policy has led to the reduction in school bullying prevalence from 25% to 11%.

Prevention programs for cyberbullying are at a more nascent stage, reflecting uncertainty about the prevalence of the practice, who is perpetrating it and from where, and how students respond when they are victimized. One study of approximately 800 parents and 1200 of their children found that although 80% of parents had set rules regarding conduct on the Internet, 85% of the children who had engaged in cyberbullying had done so from their homes. Therefore, if the bullying is reported to the police, the police could track the IP address to find the bully. However, rates vary tremendously by survey (and country) regarding student notification of adults when cyberbullied, with less than 10% of students in a Swedish survey, one-third in a Canadian survey, and a majority in an Austrian survey having reported the victimization to an adult. Many schools have established cyberbullying policies and are increasingly involved with teaching youth about guidelines for appropriate online interactions, and monitoring for cyberbullying problems. As of July 2013, 49 states (plus Washington, DC) have enacted legislation aimed to prevent bullying and 47 states (plus Washington, DC) have specific legislation regarding electronic harassment. Pediatric clinicians must be aware of local legislative action to support children in this difficult topic. (See http://www.cyberbullying.us/Bullying_and_Cyberbullying_Laws.pdf)

Bibliography is available at Expert Consult.

### 39.2 Effects of War on Children

*Isaiah D. Wexler and Eitan Kerem*

The adverse consequences of war on children are endless—death, pain, dismemberment and other physical and cognitive disabilities, acute and chronic psychological suffering, temporary and permanent loss of family members, rape, conscription into armed service, forced relocation, famine, drought, and a litany of other untoward consequences lasting for decades after hostilities have ceased. More than 1 billion children <18 yr live in countries involved in war. The majority of sexual victims in war-torn nations are <17 yr of age. The United Nations Children’s Fund (UNICEF) estimates that of the 3.6 million people killed as a result of military conflict between the years 1990 and 2003, 90% were civilian and 50% were children.

Mortality and morbidity related to the long-term effects of war and civil strife are often higher than that occurring during actual fighting. War and violence are not listed as leading causes of childhood mortality, but the regions with the highest levels of child mortality, especially among children <5 yr of age, are the same locations involved in military conflicts. Nations, especially but not limited to the least developed, devote substantial portions of their budgets to military expenditures at the expense of the healthcare infrastructure; a substantial proportion of deaths attributed to malnutrition, environmentally related infectious disease, or inadequate immunization are related to the effects of war. For example, an analysis of postwar (2003) Iraq found that mortality rates were 5.5/1,000/yr preinvasion (occurred in March 2003), and 13.2/1,000/yr for the 40 mo postinvansion; through mid-2006, there had been an estimated 654,965 fatalities above the preinvasion death rate, of which 601,027 were from violent causes. The largest group of deaths among females occurred among those <15 yr; infant and <5 yr of age mortality rates had not returned to their 1991 pre-Gulf War levels.

During wartime, customary patterns of behavior are forced to change, overcrowding is frequent, and essential resources, such as water and food staples, may be polluted or contaminated. War is associated with plagues and epidemics and novel disease entities can develop or reemerge. African nodding disease, Konzo (cassava-associated cyanide intoxication), polio, and other epidemics have been attributed to the effects of war.

The morbidity of children exposed to conflicts is significant (Table 39-2). Many more children are physically harmed than killed. Children bear the psychological scars of war resulting from exposure to violent events, loss of primary caregivers, and forced removal from their homes. During periods of war, children are more susceptible to exploitation in the forms of forced conscription as soldiers, sexual exploitation, and slavery. There are approximately 300,000 soldiers younger than the age of 18 yr who are actively participating in military conflicts worldwide. Lacking the appropriate education and socialization, the moral compass of these children is often misaligned. They are not capable of understanding the sources of conflict or why they have been targeted. Their thought processes are more concrete; it is easier for them to dehumanize their adversaries. Children, who themselves are exposed to violence and cruelty, often become the worst perpetrators of atrocities.

After cessation of hostilities, children are still at risk for life-endangering injuries from landmines and unexploded ordnance. Prior to the signing of the international treaty to ban landmines in 1997, an estimated 20,000–25,000 casualties occurred annually from landmines. In 1999, that number had decreased to 8,807 and by 2011 to 4,286. The CDC reported for a 5 yr period ending in 2006 that of the 5,741 individuals who were killed or injured by landmines or unexploded ordnance, 47.2% were children younger than the age of 18 yr. Injuries and death tended to occur while children were either playing or involved in household chores, and in contrast to adults, a large proportion of the injuries involved upper-extremity amputation. After the end of armed conflict, the continued proliferation of small arms and light weapons, which are easily handled by children, continues to take its toll on human life and hinders stabilization in postconflict societies.

#### Table 39-2

<table>
<thead>
<tr>
<th>Impact of War on Children</th>
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<tbody>
<tr>
<td><strong>PHYSICAL</strong></td>
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<tr>
<td>Death</td>
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<td>Rape</td>
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<td>Injuries</td>
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<td>Amputations and fractures</td>
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<td>Head trauma</td>
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<td>Ballistic wounds</td>
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<td>Blast injuries</td>
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<tr>
<td>Burns</td>
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<td>Chemical and biologic induced</td>
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<td>Malnutrition and starvation</td>
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<tr>
<td>Infectious disease</td>
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<tr>
<td>Displacement</td>
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<tr>
<td><strong>PSYCHOSOCIAL</strong></td>
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<tr>
<td>Loss of caregivers and family members</td>
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<tr>
<td>Separation from community</td>
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<tr>
<td>Lack of education</td>
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<tr>
<td>Inappropriate socialization</td>
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<tr>
<td>Acute stress reaction</td>
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<td>Posttraumatic stress disorder</td>
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<tr>
<td>Depression</td>
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<tr>
<td>Maladaptive behavior</td>
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<tr>
<td><strong>EXPLOITATION</strong></td>
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<tr>
<td>Coercion as soldiers</td>
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<tr>
<td>Coerced involvement in terrorist activities</td>
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<tr>
<td>Prostitution</td>
</tr>
<tr>
<td>Slavery</td>
</tr>
<tr>
<td>Forced adoption</td>
</tr>
</tbody>
</table>
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Bibliography


Department of Health and Human Services: Take a stand! Lend a hand! Stop bullying now! stopbullyingnow.hrsa.gov/kids/.


Website Resources

www.aap.org/ConnectedKids/.
SUSCEPTIBILITY OF CHILDREN IN TIMES OF WAR

Children do not have the physical or intellectual capabilities to defend themselves. It is easier for adults to victimize children than to victimize other adults. Older children’s curiosity, desire for adventure, and imperfect assessment of risk often lead them to participate in dangerous behavior. Younger children, because of their small size and immature physiology, are more susceptible to disease and starvation, and are more likely to sustain fatal injuries from ballistic projectiles and explosive devices such as mines. Blast injuries, which are now the most common cause of battle-related injuries, have a more devastating impact on children as compared to adults. Specific types of military engagement can have a disproportionate effect on children. In a survey of war-related mortality in Iraq from 2003-2008, it was found that approximately 10% of the violence-related fatalities were children. Most children succumbed to either small-arms gunfire or suicide bombs (35%). When compared to adults, a proportionately higher rate of children died as a result of the usage of indiscriminate types of weaponry such as mortars, missiles, and aircraft-delivered bombs; 40% of the total casualties in these types of attacks were children.

During times of war, there is a breakdown of social inhibitions and cultural norms. Aberrant behavior such as rape, torture, and pillaging, which would be nearly inconceivable in times of peace, is common during war. Children may be attacked or used as human shields.

The changing nature of war has adversely affected children. Conventional warfare in which armies of professional soldiers representing different countries battle each other has become less common. Intrastate conflicts in the form of civil war are more frequent. Of the approximately 200 armed conflicts occurring after World War II, three-quarters have been intrastate. These conflicts are often rooted in ethnic or religious differences, and the participants are frequently nonprofessional “irregulars” who lack discipline and accountability to higher echelons, and are directed by those who do not acknowledge or respect international accords governing warfare. Often the military resources of the antagonists are disproportionate, leading the weaker protagonist to develop compensatory tactics that can include guerilla, paramilitary, and terrorist activities, while the stronger side often resorts to the disproportionate use of force. Low-intensity conflicts have become more common. These types of conflicts are often characterized by military activities targeting civilian populations with the goal of disrupting normal routines and generating publicity for the perpetrators. Children are often victims, as this serves to maximize the impact of terrorist activity.

Terrorism and organized urban-based gang warfare violence have become more prevalent. Violence perpetrated by terrorists groups or gangs is designed to coerce and/or intimidate both individuals and entire societies. The destruction of the New York City World Trade Center Towers in 2001 and the nearly 3,000 fatalities showed that highly organized and motivated terrorists have few inhibitions and can strike anywhere. Biologic and chemical terrorism have also been realized, with the most recent example being the use of sarin gas, a deadly volatile nerve agent, in the Syrian civil war. Children are more susceptible to chemical and biologic toxins because of their higher respiratory rates, more permeable skin, and other developmental vulnerabilities (see Chapter 723).

The media has had a significant role in exacerbating the effects of war on children. Media coverage of war and terrorist events is extensive and graphic. Children, who are more impressionable than adults, often view this material in an uncontrolled fashion. Uncensored pictures of victims, unbridled violence, people in shock, or family members searching through ruins for relatives may traumatize children and even encourage inappropriate behavior. Overt broadcast propaganda glorifying war and violence may sway children to participate in militaristic or antisocial activities.

PSYCHOLOGIC IMPACT OF WAR

Exposure to war and violence can have a significant impact on a child’s psychosocial development. Displacement, loss of caregivers, physical suffering, and the lack of appropriate socialization all contribute to abnormal child development (see Table 39-2). Often the reactions are age-specific (Table 39-3). Preschoolers may have an increase in somatic complaints and sleep disturbances, and have acting-out behavior such as tantrums or excessively clinging behavior. School-age children will show regressive behavior such as enuresis and thumb sucking. They, too, have an increase in somatic complaints; there is often a negative impact on school performance. For teenagers, psychological withdrawal and depression are common. Adolescents often exhibit trauma-stimulated acting-out behavior. Motivated by the desire for revenge, they may be quick to join in the violence and contribute to the continuation of conflict.

There is an increased incidence of both acute stress reactions and PTSD (see Chapter 25). The true incidence is difficult to assess because of the heterogeneous nature of war, degree of exposure to violence, and methodological challenges related to the precise characterization of PTSD. The incidence of PTSD among children and adolescents living in Middle East countries that have experienced substantial armed conflict appear to be high: 5-8% in Israel, 23-70% in Palestine, and 10-30% in Iraq. Risk factors for having a more serious psychological response to a violent event include severity of the incident, personal involvement (physical injury, proximity, loss of a relative), prior history of exposure to traumatic events, female gender, and a dysfunctional parental response to the same event. It is not unusual for children to develop PTSD many years after the traumatic event. Children do not have to be directly exposed to violent activity, and media coverage of terrorist events may be sufficient to trigger PTSD.

The trauma experienced by children during war can have lifelong effects. Studies on children imprisoned in concentration camps or evacuated from their homes in London during the Battle of Britain show that these individuals were at greater risk for PTSD, anxiety disorders, and a higher level of dissatisfaction with life. Individuals who suffered wartime trauma can pass on certain traits to their children, including a greater propensity for PTSD. However, children are resilient. With appropriate support from family and community

<table>
<thead>
<tr>
<th>Table 39-3</th>
<th>Manifestations of Stress Reactions in Children and Adolescents Exposed to War, Terrorism, and Urban Violence</th>
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<tbody>
<tr>
<td>CHILDREN ≤ 6 YEARS</td>
<td>Excessive fear of separation</td>
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<tr>
<td></td>
<td>Clinging behavior</td>
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<td></td>
<td>Uncontrollable crying or screaming</td>
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<td>Freezing (persistent immobility)</td>
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<td>Sleep disorders</td>
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<td>Terrified affect</td>
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<td></td>
<td>Regressive behavior</td>
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<td></td>
<td>Abnormally aggressive or violent behavior</td>
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<tr>
<td></td>
<td>Irrational fears</td>
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<tr>
<td></td>
<td>Regressive and childish behavior</td>
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<tr>
<td></td>
<td>Expressions of fearfulness, withdrawal, and worry</td>
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<tr>
<td>CHILDREN 7-11 YEARS</td>
<td>Decline in school performance</td>
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<td></td>
<td>Truancy</td>
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<td></td>
<td>Sleep disorders</td>
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<td>Somatization</td>
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<td>Depressive affect</td>
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<td>Abnormally aggressive behavior</td>
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<td>Regressive and childish behavior</td>
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<td>Expressions of fearfulness, withdrawal, and worry</td>
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<tr>
<td>ADOLESCENTS 12-17 YEARS</td>
<td>Decline in school performance</td>
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<tr>
<td></td>
<td>Sleep disturbances</td>
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<td></td>
<td>Flashbacks</td>
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<td>Emotional numbness</td>
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<td>Antisocial behavior</td>
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<td></td>
<td>Substance abuse</td>
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<td>Revenge fantasies</td>
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<td></td>
<td>Suicidal ideation</td>
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<td></td>
<td>Withdrawal</td>
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together with timely and intensive psychological intervention, children can recover and lead normal, productive lives despite the searing trauma that they may have experienced.

**EFFORTS TO PROTECT CHILDREN FROM THE EFFECTS OF WAR**

**International Conventions**

War and terror violate the human rights of children, including the right to life, the right to be nurtured and protected, the right to develop appropriately, the right to be with family and community, and the right to a healthy existence. Several international treaties and conventions have been ratified, beginning with the Fourth Geneva Convention (1949) that set forth guidelines regarding appropriate treatment of children in times of war. The United Nations Convention on the Rights of the Child (1990) delineated specific human rights inherent to every child (defined as any individual younger than the age of 18 yr), and the subsequent First Optional Protocol (2000), which prohibits conscripting or recruiting children for military activities. The Rome Statute of the International Criminal Court, which was enacted in 2002, declared that the conscription or enlistment of children younger than the age of 15 yr is a prosecutable war crime. As of 2010, a decade since their passage, the number of armed conflicts in which children were serving as soldiers had decreased from 36 to 16 worldwide.

Although these treaties and conventions define the extent of protection afforded to children, the means of enforcement available to the international community is limited. Individuals, motivated by religious fervor, nationalistic zeal, or ethnic xenophobia, are unlikely to curb their activities because of fear of prosecution. These treaties better serve in heightening awareness regarding the protected status of children in wartime, and perhaps deter high-ranking leaders who fear being held accountable for war crimes.

**Humanitarian Efforts**

Several organizations, either nongovernmental or under the auspices of the United Nations, are involved in mitigating the effects of war on children. These organizations, which include the International Red Cross, UNICEF, United Nations Refugee Agency (UNCHR), International Rescue Committee, World Health Organization, and Médecins Sans Frontières (Doctors Without Borders), have had a significant impact on reducing violence-related casualties in war-torn regions. The infusion of humanitarian aid into developing countries often improves overall mortality and morbidity by increasing the level of medical and social services available to the general population. Other organizations, such as Amnesty International, Stockholm International Peace Research Institute, and Physicians for Human Rights, actively monitor human rights abuses involving children and other civilian groups. In 2005, the United Nations Security Council approved the establishment of a monitoring and reporting system designed to protect children exposed to war. United Nations–led task forces conduct active surveillance in war-stricken regions reporting on the 6 grave violations against children during armed conflict: the killing or injuring of children, recruitment of child soldiers, attacks directed against schools or hospitals, sexual violence against children, abduction of children, and denial of humanitarian access for children.

**THE ROLE OF PEDIATRICIANS AND ALLIED HEALTH PROFESSIONALS**

War is a chronic condition and health providers need to be prepared to treat childhood casualties resulting from military or terrorist activity as well as caring for children suffering from the aftermath of war or related violence. Community and hospital pediatricians need to be involved in community disaster planning. General disaster planning should not ignore the unique needs and requirements of children; in planning for a possible chemical attack, appropriate resuscitation equipment suitable for children needs to be stockpiled. The signs of biologic infection or chemical intoxication are different for children, and pediatricians and emergency personnel need to be aware of these differences (see Chapters 719 and 723). Surveys of pediatricians and other healthcare providers indicate that many feel unprepared for bioterrorism attacks. Professional organizations such as the American Academy of Pediatrics and the CDC have published position papers; there is a special section in the American Academy of Pediatrics Red Book that presents guidelines for treating specific pathogens likely to be utilized in biologic warfare. In regions where violent terrorist activity is likely, pediatricians, nurses, and rescue personnel should consider becoming certified in the Red Cross Basic and Advanced Trauma Life Support.

Pediatricians need to be cognizant of the effects that war and terror can have on parents and children. Parents, who themselves are under tremendous strain, may not be sensitive to the effects that the same stressors have on their children. Pediatricians should draw out both parents and children, and encourage them to talk freely about their feelings. Child healthcare providers can be instrumental in educating parents to be more aware of inappropriate responses by children to war and violence. When necessary, pediatricians can serve their families by referring them to appropriate support services.

Just as it is important to administer first aid for physical trauma, it is also critical to provide psychologic first aid to victims of trauma. An excellent source of online information for both providers and caregivers is provided by the National Child Traumatic Stress Network (www.nctsn.org). In day-to-day patient interactions, a pediatrician is most likely to confront situations related to stress reactions such as PTSD or depressive disorders. Recognition of PTSD is essential so that early treatment can be initiated. *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) stipulates that for a diagnosis of PTSD, there has to be manifestations from each of four symptom clusters: intrusion, avoidance, negative alterations in cognitions and mood, and alterations in arousal and reactivity. The DSM-V also established a special preschool subtype of PTSD which has the same four symptom clusters but with specific manifestations that are typical of preschoolers exposed to trauma (see Chapter 25). Clues to the presence of PTSD and acute anxiety reactions include changes in behavior, school performance, affect, and sleep patterns, and an increase in somatic complaints. Even when the triggering event is neither temporally nor physically proximate, it should not dissuade the pediatrician from making an appropriate referral to mental health professionals who are expert in childhood stress disorders.

Medical professional standards demand from each physician that the physician treat all patients equitably without regard to their background. Both international law and professional medical societies ban physicians from actively participating in torture or other activities that infringe on human rights, including those of children. It is difficult to countenance any situation in which a health professional, even acting as a representative of his or her country, might directly or indirectly injure a minor.

Health professionals have an important role in preventing the atrocities that occur to children. In their role as advocates for the rights of children, pediatricians can be instrumental in focusing public attention on the precarious situation of children exposed to brutality and mayhem that are part and parcel of organized violence. They can promulgate the message that war and terror should not be allowed to rob children of their childhood.

*Bibliography is available at Expert Consult.*
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Drury J, Williams R: Children and young people who are refugees, internally displaced persons or survivors or perpetrators of war, mass violence and terrorism, Curr Opin Psychiatry 25(4):277–284, 2012.
The maltreatment (including abuse and neglect) of children is a pervasive problem in nations throughout the world (Fig. 40-1), with short- and long-term physical and mental health and social consequences to the child, family, community, and society at-large. In addition to the child healthcare professionals’ responsibility to identify maltreated children and help ensure their protection and health, they should assume vital roles related to prevention, treatment, and advocacy. Rates and policies vary greatly among nations and often within nations. Rates of maltreatment and provision of services are affected by the overall policies of the country, province, or state governing recognition and responses to child abuse and neglect. Two broad approaches have been identified: a child and family welfare approach, with a focus on the family as a whole, and a child safety approach, with the focus on the child perceived to be at risk. The United States has primarily had a child safety approach.

DEFINITIONS

Abuse is defined as acts of commission and neglect as acts of omission. The U.S. government defines child abuse as “any recent act or failure to act on the part of a parent or caretaker, which results in death, serious physical or emotional harm, sexual abuse or exploitation, or an act or failure to act which presents an imminent risk of serious harm.” Some states in the United States also include other household members. Children may be found in situations in which no actual harm has occurred and no imminent risk of serious harm is evident, but potential harm may be a concern. Many states include potential harm in their child abuse laws. Consideration of potential harm enables preventive intervention, although predicting potential harm is inherently difficult. Two aspects should be considered. One is the likelihood of harm; the other is the severity of that harm.

Physical abuse includes beating, shaking, burning, and biting. Corporal punishment in any form is increasingly being prohibited. The Global Initiative to End All Corporal Punishment of Children reported that 33 countries have prohibited corporal punishment in all settings, including the home. Governments in at least an additional 18 countries are publicly committed to prohibition in all settings. The majority of countries have prohibited corporal punishment in settings outside the home—in schools (117 countries), in penal institutions (121 countries), and as a sentence of the courts (157 countries). In the United States, corporal punishment in the home is lawful in all states, but 31 states have banned corporal punishment in public schools and the Supreme Court has ruled it unlawful as punishment for a crime.

Internationally, a high proportion of children continue to experience corporal punishment. At the beginning of 2013, 33 countries had banned all corporal punishment, while in 165 some form of corporal punishment is permitted, including 41 countries in which children can be sentenced to corporal punishment for committing a crime.

The threshold for defining corporal punishment as abuse is unclear. One can consider any injury beyond transient redness as abuse. If parents spank a child, it should be limited to the buttocks, should occur over clothing, and should never involve the head and neck. When parents use objects other than a hand, the potential for serious harm increases. Acts of serious violence (e.g., throwing a hard object, slapping an infant’s face) should be seen as abusive even if no injury ensues; significant risk of harm exists. Although some child healthcare professionals think that hitting is acceptable under limited conditions, almost all believe that more constructive approaches to discipline are preferable. Although many think that hitting a child should never be acceptable, and many studies have documented the potential harm, there remains a reluctance in the United States to label hitting as abuse unless there is an injury. It is clear that the emotional impact of being hit may leave the most worrisome scar, long after the bruises fade and the fracture heals.

Sexual abuse has been defined as “the involvement of dependent, developmentally immature children and adolescents in sexual activities which they do not fully comprehend, to which they are unable to give consent, or that violate the social taboos of family roles.” Sexual abuse includes exposure to sexually explicit materials, oral-genital contact, genital-to-genital contact, genital-to-anal contact, and genital fondling. Any touching of “private parts” by parents or caregivers in a context other than necessary care is inappropriate.

Neglect refers to omissions in care, resulting in actual or potential harm. Omissions include inadequate healthcare, education, supervision, protection from hazards in the environment, and unmet physical needs (e.g., clothing, food) and emotional support. A preferable alternative to focusing on caregiver omissions is to instead consider the basic needs (or rights) of children (e.g., adequate food, clothing, shelter, healthcare, education, nurturance); neglect occurs when a need is not adequately met and results in actual or potential harm, whatever the reasons. A child whose health is jeopardized or harmed by not receiving necessary care experiences medical neglect. Not all such situations

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Figure 40-1 Percentage of children ages 2-14 yr who experienced any violent discipline (physical punishment and/or psychological aggression) in the past month, by country. (From UNICEF, Child disciplinary practices at home: evidence from a range of low- and middle-income countries, 2010. http://www.childinfo.org/discipline.html.)
necessarily require a report to child protective services (CPS); less-intrusive initial efforts may be appropriate.

Psychological abuse includes verbal abuse and humiliation and acts that scare or terrorize a child. Although this form of abuse may be extremely harmful to children, resulting in depression, anxiety, poor self-esteem, or lack of empathy, CPS seldom becomes involved because of the difficulty in proving such allegations. Child healthcare professionals should still carefully consider this form of maltreatment, even if the concern fails to reach a legal or agency threshold for reporting. These children and families can benefit from counseling and social support. Many children experience more than 1 form of maltreatment; CPS may be more likely to address psychological abuse in the context of other forms of maltreatment.

Internationally, problems of trafficking in children, for purposes of cheap labor and/or sexual exploitation, expose children to all of the forms of abuse just noted.

INCIDENCE AND PREVALENCE

Global Situation
Child abuse and neglect are not rare and occur worldwide. Based on international studies, the World Health Organization (WHO) has estimated that approximately 20% of women and 5-10% of men report being sexually abused as children, while 25-50% of all children report being physically abused. Many children experience emotional abuse and neglect. Rates of child abuse overall and both corporal and psychological vary greatly by this sample of lower- and middle-income nations. Although more difficult to detect and therefore probably underestimated, reports of psychological abuse tend to be somewhat higher than those of physical abuse (Fig. 40-2).

Situation in the United States
Abuse and neglect mostly occur behind closed doors and often are a well-kept secret. Nevertheless, there were 3.4 million reports to CPS involving 6.2 million children in the United States in 2011. Of the 681,000 children with substantiated reports, 78.5% experienced neglect, 17.6% physical abuse, 9.1% sexual abuse, and 9% psychological maltreatment. These rates of substantiated maltreatment continue a trend where neglect has remained at a steady rate since the early 1990s, whereas both sexual and physical abuse rates have declined by approximately 50%. Medical personnel made 8.4% of all reports. The rate of hospitalized children with serious physical abuse has not declined in recent years, raising the possibility of CPS trends not necessarily representing a true decline.

Etiology
Child maltreatment seldom has a single cause; rather, multiple and interacting biopsychosocial risk factors at 4 levels usually exist. To illustrate, at the individual level, a child’s disability or a parent’s depression or substance abuse predispose a child to maltreatment. At the familial level, intimate partner (or domestic) violence presents risks for children. Influential community factors include stressors such as dangerous neighborhoods or a lack of recreational facilities. Professional inaction may contribute to neglect, such as when the treatment plan is not clearly communicated. Broad societal factors, such as poverty and its associated burdens, also contribute to maltreatment. WHO estimates the rate of homicide of children is approximately 2-fold higher in low-income compared to high-income countries (2.58 vs. 1.21 per 100,000 population), but clearly homicide occurs in high-income countries. Children in all social classes can be maltreated, and child healthcare professionals need to guard against biases concerning low-income families.

Protective factors, such as family supports, or a mother’s concern for her child, may buffer risk factors and protect children from maltreatment. Identifying and building on protective factors can be vital to intervening effectively. One can say to a parent, for example, “I can see how much you love _____. What can we do to keep her out of the hospital?” Child maltreatment results from a complex interplay among risk and protective factors. A single mother who has a colicky baby and who recently lost her job is at risk for maltreatment, but a loving grandmother may be protective. A good understanding of factors that contribute to maltreatment, as well as those that are protective, should guide an appropriate response.

Clinical Manifestations
Child abuse and neglect can manifest in many different ways. With regard to physical abuse, a critical element is the lack of a plausible history other than inflicted trauma. Signs of abuse may precede the eventual diagnosis of child abuse. These sentinel injuries may be noted in approximately 25% of abused infants and may precede the diagnosis by weeks or even months from the sentinel event. Bruising and intraoral injury, in addition to symptoms of an acute life-threatening event, may be early clues of abuse. As with any medical condition, the onus is on the clinician to carefully consider the differential diagnosis and not jump to conclusions.

Bruises are the most common manifestation of physical abuse. Features suggestive of inflicted bruises include (a) bruising in a preambulatory infant (occurring in just 2% of infants), (b) bruising of padded and less-exposed areas (buttocks, cheeks, under the chin, genitalia), (c) patterned bruising or burns conforming to shape of an object or lacerations along the wrists (Table 40-1, Figs. 40-3 and 40-4), and (d) multiple bruises, especially if clearly of different ages. Earlier suggestions for estimating the age of bruises have been discredited. It is very difficult to precisely determine the ages of bruises.

Other conditions, such as birthmarks and mongolian spots can be confused with bruises and abuse. These skin markings are not tender
Figure 40-3 A variety of instruments may be used to inflict injury on a child. Often the choice of an instrument is a matter of convenience. Marks tend to silhouette or outline the shape of the instrument. The possibility of intentional trauma should prompt a high degree of suspicion when injuries to a child are geometric, paired, mirrored, of various ages or types, or on relatively protected parts of the body. Early recognition of intentional trauma is important to provide therapy and prevent escalation to more serious injury.

Table 40-1 Injury Patterns

<table>
<thead>
<tr>
<th>METHOD OF INJURY/IMPLEMENT</th>
<th>PATTERN OBSERVED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grip/grab</td>
<td>Relatively round marks that correspond with fingertips and/or thumb</td>
</tr>
<tr>
<td>Closed-fist punch</td>
<td>Series of round bruises that correspond with the knuckles of the hand</td>
</tr>
<tr>
<td>Slap</td>
<td>Parallel, linear bruises (usually petechial) separated by areas of central sparing</td>
</tr>
<tr>
<td>Belt/electrical cord</td>
<td>Loop marks or parallel lines of petechiae (the width of the belt/cord) with central sparing; may see triangular marks from the end of the belt, small circular lesions caused by the holes in the tongue of the belt, and/or a buckle pattern</td>
</tr>
<tr>
<td>Rope</td>
<td>Areas of bruising interspersed with areas of abrasion</td>
</tr>
<tr>
<td>Other objects/household implements</td>
<td>Injury in shape of object/implement (e.g., rods, switches, and wires cause linear bruising)</td>
</tr>
<tr>
<td>Human bite</td>
<td>Two arches forming a circular or oval shape, may cause bruising and/or abrasion</td>
</tr>
<tr>
<td>Strangulation</td>
<td>Petechiae of the head and/or neck, including mucous membranes; may see subconjunctival hemorrhages</td>
</tr>
<tr>
<td>Binding/ligature</td>
<td>Marks around the wrists, ankles, or neck; sometimes accompanied by petechiae or edema distal to the ligature mark or Marks adjacent to the mouth if the child has been gagged</td>
</tr>
<tr>
<td>Excessive hincar (punishment by kneeling on salt or other rough substance)</td>
<td>Abrasions/burns, especially to knees</td>
</tr>
<tr>
<td>Hair pulling</td>
<td>Traumatic alopecia; may see petechiae on underlying scalp, or swelling or tenderness of the scalp (from subgaleal hematoma)</td>
</tr>
<tr>
<td>Tattooing or intentional scarring</td>
<td>Abusive cases have been described, but can also be a cultural phenomenon (e.g., Maori body ornamentation)</td>
</tr>
</tbody>
</table>

and do not rapidly change color or size. An underlying medical explanation for bruises may exist, such as connective tissue disorders or blood dyscrasias (see Chapters 476, 477, and 484). The history or examination usually provides clues to these conditions. Henoch-Schönlein purpura, the most common vasculitis in young children, may be confused with abuse. The pattern and location of bruises caused by abuse are usually different from those caused by a coagulopathy. Noninflicted bruises are characteristically anterior and over bony prominences, such as chin, ankles, elbows, shins, and forehead. The presence of a medical disorder does not preclude abuse.

Cultural practices can cause bruising. Cao gio, or coining, is a South-east Asian folkloric therapy. A hard object is vigorously rubbed on the skin, causing petechiae or purpura. Cupping is another approach, popular in the Middle East. A heated glass is applied to the skin, often on the back. As it cools, a vacuum forms, leading to perfectly circular bruises. The context here is important, and such circumstances should not be considered abusive (see Chapter 4).

A careful history of bleeding problems in the patient and first degree relatives is needed. If a bleeding disorder is suspected, a complete blood count including platelet count, prothrombin time, and partial thromboplastin time should be obtained. More extensive testing, such as factors VIII, IX, and XI activity and a von Willebrand evaluation, should be considered in consultation with a hematologist.

Bites have a characteristic pattern of 1 or 2 opposing arches with multiple bruises (see Fig. 40-3). They can be inflicted by an adult, another child, an animal, or the patient. Bites by a child (younger than approximately 8 yr with primary teeth) typically have a distance of less than 2.5 cm between the canines—often the most prominent bruises.
A child is likely to try to rapidly escape from a hot object; thus burns that are extensive and deep reflect more than fleeting contact and are suggestive of abuse (Fig. 40-5).

Several conditions mimic abusive burns, such as brushing against a hot radiator, car seat burns, hemangiomas, and folk remedies, such as moxibustion. Impetigo may resemble cigarette burns. Cigarette burns are usually 7-10 mm across, whereas impetigo has lesions of varying size (see Chapter 665.1). Noninflicted cigarette burns are usually oval and superficial.

Neglect frequently contributes to childhood burns. Children, home alone, may be burned in house fires. A parent taking drugs may cause a fire and may be unable to protect a child. Exploring children may pull hot liquids left unattended onto themselves. Liquids cool as they flow downward so that the burn is most severe and broad proximally. If the child is wearing a diaper or clothing, the fabric may absorb the

The appearance of animal bites is variable; they usually have narrower arches than human bites and are often deep (see Chapter 724). Self-inflicted bites are on accessible areas, particularly the hands. Adult bites raise concern for abuse. Multiple bites by another child suggest inadequate supervision and neglect.

**Burns** may be inflicted or a result of inadequate supervision. Scalding burns may result from immersion or splash. Immersion burns, when a child is forcibly held in hot water, show clear delineation between the burned and healthy skin, and uniform depth. They may have a sock or glove distribution. Splash marks are usually absent, unlike when a child inadvertently encounters hot water. Symmetric burns are especially suggestive of abuse as are burns of the buttocks and perineum. Although most often accidental, splash burn may also result from abuse. Burns from hot objects such as curling irons, radiators, steam irons, metal grids, hot knives, and cigarettes leave patterns representing the object. A child is likely to try to rapidly escape from a hot object; thus burns that are extensive and deep reflect more than fleeting contact and are suggestive of abuse (Fig. 40-5).

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![Figure 40-4 Marks from heated objects cause burns in a pattern that duplicates that of the object. Familiarity with the common heated objects that are used to traumatize children facilitates recognition of possible intentional injuries. The location of the burn is important in determining its cause. Children tend to explore surfaces with the palmar surface of the hand and rarely touch a heated object repeatedly or for a long time.](image1)

![Figure 40-5 Immersion injury patterns. A, Sparing of the flexor creases. B, Immersion “stocking” burn. C, Immersion “glove” burn. D, Immersion buttocks burn. (From Jenny C: Child abuse and neglect: diagnosis, treatment, and evidence, Philadelphia, 2011, Saunders, p. 225, Fig. 28-3.)](image2)
hot water and cause burns worse than otherwise expected. Some circumstances are difficult to foresee, and a single burn resulting from a momentary lapse in supervision should not automatically be seen as neglectful parenting. Concluding whether a burn was inflicted depends on the history, burn pattern, and the child’s capabilities. A delay in seeking healthcare may result from the burn initially appearing minor, before blistering or becoming infected. This circumstance may represent reasonable behavior and should not be automatically deemed neglectful. A home investigation is often valuable (e.g., testing the water temperature). 

Fractures that strongly suggest abuse include classic metaphyseal lesions, posterior rib fractures, and fractures of the scapula, sternum, and spinous processes, especially in young children (Table 40-2). These fractures all require more force than would be expected from a minor fall or routine handling and activities of a child. Rib and sternal fractures rarely result from cardiopulmonary resuscitation, even when performed by untrained adults. It is possible, however, that the recommended 2-finger or 2-thumb technique recommended for infants since 2005 may produce anterolateral rib fractures. In abused infants, rib (Fig. 40-6), metaphyseal (Fig. 40-7), and skull fractures are most common. Femoral and humeral fractures in nonambulatory infants are also highly suggestive for abuse. With increasing mobility and running, toddlers can fall with enough rotational force to cause a spiral, femoral fracture. Multiple fractures in various stages of healing are suggestive of abuse; nevertheless, underlying conditions need to be considered. Clavicular, femoral, supracondylar humeral, and distal extremity fractures in children older than 2 yr are most likely noninflicted unless they are multiple or accompanied by other signs of abuse. Few fractures are pathognomonic of abuse; all must be considered in light of the history.

<table>
<thead>
<tr>
<th>Table 40-2</th>
<th>Skeletal Injuries from Abuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-specificity findings</td>
<td></td>
</tr>
<tr>
<td>• Classic metaphyseal corner lesions</td>
<td></td>
</tr>
<tr>
<td>• Posterior rib fracture</td>
<td></td>
</tr>
<tr>
<td>• Scapular fracture</td>
<td></td>
</tr>
<tr>
<td>• Sternal fracture</td>
<td></td>
</tr>
<tr>
<td>• Spinous process fracture</td>
<td></td>
</tr>
<tr>
<td>• First rib fracture</td>
<td></td>
</tr>
<tr>
<td>Moderate-specificity findings</td>
<td></td>
</tr>
<tr>
<td>• Multiple fractures</td>
<td></td>
</tr>
<tr>
<td>• Fractures of differing age</td>
<td></td>
</tr>
<tr>
<td>• Spine fracture</td>
<td></td>
</tr>
<tr>
<td>• Complex skull fracture</td>
<td></td>
</tr>
<tr>
<td>• Physeal fractures of the long bones</td>
<td></td>
</tr>
<tr>
<td>• Digital fractures</td>
<td></td>
</tr>
<tr>
<td>Low-specificity findings</td>
<td></td>
</tr>
<tr>
<td>• Diaphyseal fractures of the long bones</td>
<td></td>
</tr>
<tr>
<td>• Simple skull fractures</td>
<td></td>
</tr>
<tr>
<td>• Clavicle fracture</td>
<td></td>
</tr>
</tbody>
</table>

Modified from Kleinman PK. Diagnostic imaging of child abuse, ed 2, St. Louis, 1998, Mosby.

Figure 40-6 A high-detail oblique view of the ribs of a 6 mo old infant shows multiple healing posteromedial rib fractures (arrowheads). The level of detail in this image is far greater than what would be present on a standard chest radiograph. (From Dwek JR. The radiographic approach to child abuse. Clin Orthop Relat Res 469:776-789, 2011, p. 780, Fig. 4.)

Figure 40-7 A, Metaphyseal fracture of the distal tibia in a 3 mo old infant admitted to the hospital with severe head injury. There is also periosteal new bone formation of the tibia, perhaps from previous injury. B, Bone scan of same infant. Initial chest x-ray showed a single fracture of the right posterior 4th rib. A radionuclide bone scan performed 2 days later revealed multiple previously unrecognized fractures of the posterior and lateral ribs. C, Follow-up radiographs 2 wk later showed multiple healing rib fractures. This pattern of fracture is highly specific for child abuse. The mechanism of these injuries is usually violent squeezing of the chest.
The differential diagnosis includes conditions that increase susceptibility to fractures, such as osteopenia of prematurity and osteogenesis imperfecta, metabolic and nutritional disorders (e.g., scurvy, copper deficiency, rickets), renal osteodystrophy, osteomyelitis, congenital syphilis, congenital insensitivity to pain, Caffey disease, and neoplasia. Some have pointed to possible rickets and low but subclinical levels of vitamin D as being responsible for fractures thought to be abusive. The evidence to date does not support this supposition. Features of congenital or metabolic conditions associated with nonabusive fractures include family history of recurrent fractures after minor trauma, abnormally shaped cranium, dentinogenesis imperfecta, blue sclera, wormian bones, craniotabes, ligamentous laxity, bowed legs, hernia, and translucent skin. Subperiosteal new bone formation is a nonspecific finding seen in infectious, traumatic, and metabolic disorders. In young infants, new bone formation may be a normal physiologic finding, usually bilateral, symmetric, and less than 2 mm in depth.

The evaluation of a fracture should include a skeletal survey in children <2 yr of age when abuse seems possible. Multiple films with different views are needed (Table 40-3); “babygrams” (1 or 2 films of the entire body) should be avoided. If the survey is normal, but concern for an occult injury remains, a radionucleotide bone scan should be performed to detect a possible acute injury. Follow-up films after 2 wk may also reveal fractures not apparent initially.

In corroborating the history and the injury, the age of a fracture can be crudely estimated (Table 40-4). Soft-tissue swelling subsides in 2–21 days. Periosteal new bone is visible within 10–21 days. Soft callus can be visible after 10 days and hard callus between 14–90 days. These time frames are shorter in infancy and longer in children with poor nutritional status or a chronic underlying disease. Fractures of flat bones such as the skull do not form callus and cannot be aged, although soft-tissue swelling indicates approximate recency (i.e., within the prior week).

Abusive head trauma (AHT) results in the most significant morbidity and mortality. Abusive injury may be caused by direct impact, asphyxia, or shaking. Subdural hematomas (Fig. 40-8), retinal hemorrhages (Fig. 40-9), particularly when extensive and involving multiple layers, and diffuse axonal injury strongly suggest AHT, especially when they co-occur. The poor neck muscle tone and relatively large heads of infants make them vulnerable to acceleration–deceleration forces associated with shaking, leading to AHT. Children may lack external signs of injury, even with serious intracranial trauma. Signs and symptoms may be nonspecific, ranging from lethargy, vomiting (without diarrhea), changing neurologic status or seizures, and coma. In all preverbal children, an index of suspicion for AHT should exist when children present with these signs and symptoms. Asymptomatic subdural hemorrhage may occur after vaginal or cesarean birth. These resolve by 1 mo of age and prior to resolution the infant remains asymptomatic.

Skull fractures are common in abuse, reflecting impact injury. There is no specific pattern of skull fracture that is diagnostic of abuse. Acute intracranial trauma is best evaluated via initial and follow-up CT. MRIs are helpful in differentiating extra axial fluid, determining timing of injuries, assessing parenchymal injury, and identifying vascular anomalies. MRIs are best obtained 5–7 days after an acute injury. Glutaric aciduria type 1 can present with intracranial bleeding and should be considered. Other causes of subdural hemorrhage in infants include arteriovenous malformations, coagulopathies, birth trauma, tumor, or infections. When AHT is suspected, injuries elsewhere—skeletal and abdominal—should be ruled out.

### Table 40-3 Skeletal Survey for Infants and Children Under 2 Yr of Age

<table>
<thead>
<tr>
<th>Category</th>
<th>Technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anteroposterior (AP) and lateral of skull (Townes view optional; add if any fracture seen)</td>
<td></td>
</tr>
<tr>
<td>Lateral spine (C-spine may be included on skull radiographs; AP spine is included on AP chest and AP pelvis to include entire spine)</td>
<td></td>
</tr>
<tr>
<td>AP, right posterior oblique, left posterior oblique of chest—rib technique</td>
<td></td>
</tr>
<tr>
<td>AP pelvis</td>
<td></td>
</tr>
<tr>
<td>AP of each femur</td>
<td></td>
</tr>
<tr>
<td>AP of each leg</td>
<td></td>
</tr>
<tr>
<td>AP of each humerus</td>
<td></td>
</tr>
<tr>
<td>AP of each forearm</td>
<td></td>
</tr>
<tr>
<td>Posteroanterior of each hand</td>
<td></td>
</tr>
<tr>
<td>AP (dorsoventral) of each foot</td>
<td></td>
</tr>
</tbody>
</table>

*Images are checked by a radiologist before the patient leaves. Poorly positioned or otherwise suboptimal images should be repeated. Lateral views are added for positive or equivocal findings in the extremities. Coned views of positive or equivocal findings (i.e., at the ends of the long bones, ribs) may be obtained.


### Table 40-4 Timetable of Radiologic Changes in Children’s Fractures

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>EARLY</th>
<th>PEAK</th>
<th>LATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Resolution of soft-tissue swelling</td>
<td>2–5 days</td>
<td>4-10 days</td>
<td>10-21 days</td>
</tr>
<tr>
<td>2. Subperiosteal new bone formation</td>
<td>4-10 days</td>
<td>10-14 days</td>
<td>14-21 day</td>
</tr>
<tr>
<td>3. Loss of fracture line definition, days</td>
<td>10-14 days</td>
<td>14-21 days</td>
<td></td>
</tr>
<tr>
<td>4. Soft callus</td>
<td>10-14 days</td>
<td>14-21 days</td>
<td></td>
</tr>
<tr>
<td>5. Hard callus</td>
<td>14–21 days</td>
<td>21-42 days</td>
<td>42-90 days</td>
</tr>
<tr>
<td>6. Remodeling of fracture</td>
<td>3 mo</td>
<td>1 yr</td>
<td>2 yr to physeal closure</td>
</tr>
</tbody>
</table>

*Repetitive injuries may prolong categories 1, 2, 5, and 6.

Retinal hemorrhages are an important marker of AHT (see Fig. 40-9). Whenever AHT is being considered, a dilated indirect eye examination by a pediatric ophthalmologist should be performed. Although retinal hemorrhages can be found in other conditions, hemorrhages that are multiple, involve more than one layer of the retina, and extend to the periphery (outside the posterior pole) are very suspicious for abuse. The mechanism is likely repeated acceleration–deceleration as a consequence of shaking. Traumatic retinoschisis points strongly to abuse.

There are other causes of retinal hemorrhages, although the pattern is usually different than that seen in child abuse. After normal spontaneous vaginal delivery, 25% of term neonates may have retinal hemorrhages (lower with cesarean section, higher with vacuum assisted delivery). These hemorrhages are in the posterior pole and are intra-retinal; 80% resolve by 10 days, 100% by 6–8 wk. Coagulopathies (particularly leukemia), retinal diseases, carbon monoxide poisoning, or glutaric aciduria may be responsible. Severe noninflicted direct crush injury to the head can rarely cause an extensive hemorrhagic retinopathy. Cardiopulmonary resuscitation rarely, if ever, causes retinal hemorrhage in infants and children; if present, there are a few hemorrhages in the posterior pole. Hemoglobinopathies, diabetes mellitus, routine play, minor noninflicted head trauma, and vaccinations do not appear to cause retinal hemorrhage in children. Severe coughing or seizures rarely cause retinal hemorrhages that could be confused with AHT. Retinal hemorrhages are rare in children with increased cranial pressure.

The dilemma frequently posed is whether minor, “everyday” forces can explain the findings seen in AHT. Simple linear skull fractures in the absence of other suggestive evidence can be explained by a short fall, although even that is rare (1–2%), and underlying brain injury from short falls is exceedingly rare. Timing of brain injuries in cases of abuse is not precise. In fatal cases, however, the trauma most likely occurred very soon before the child became symptomatic.

Other manifestations of AHT may be seen. “Raccoon” eyes occur in association with subgaleal hematomas after traction on the anterior hair and scalp or after a blow to the forehead. Neuroblastoma can present similarly, and should be considered (see Chapter 498). Bruises from attempted strangulation may be visible on the neck. Choking or suffocation can cause hypoxic brain injury, often with no external signs.

Abdominal trauma accounts for significant morbidity and mortality in abused children. Young children are especially vulnerable because of their relatively large abdomens and lax abdominal musculature. A forceful blow or kick can cause hematomas of solid organs (liver, spleen, kidney) from compression against the spine, as well as hematoma (duodenal) or rupture (stomach) of hollow organs. Intraabdominal bleeding may result from trauma to an organ or from shearing of a vessel. More than one organ may be affected. Children may present with cardiovascular failure or an acute condition of the abdomen, often after a delay in care. Bilious vomiting without fever or peritoneal irritation suggests a duodenal hematoma, often caused by abuse.

The manifestations of abdominal trauma are often subtle, even with severe injuries. Bruising of the abdominal wall is unusual, and symptoms may evolve slowly. Delayed perforation may occur days after the injury; bowel strictures or a pancreatic pseudocyst may occur weeks or months later. Child healthcare professionals should consider screening for occult abdominal trauma when other evidence of physical abuse exists. Screening should include liver and pancreatic enzyme levels, and testing urine for blood. Children with lab results indicating possible injury should have abdominal CT performed. CT or ultrasound should also be performed if there is concern about possible splenic, adrenal, or reproductive organ injury.

Neglect is the most prevalent form of child maltreatment, with potentially severe and lasting sequelae. It may manifest in many ways, depending on which needs are not adequately met. Nonadherence to medical treatment may aggravate the condition, as may a delay in seeking care. Inadequate food may manifest as impaired growth; inattention to obesity may compound that problem. Poor hygiene may contribute to infected cuts or lesions. Inadequate supervision contributes to injuries and ingestions. Children’s needs for mental healthcare, dental care, and other health-related needs may be unmet, manifesting as neglect in those areas. Educational needs, particularly for children with learning disabilities, are often not met.

The evaluation of possible neglect requires addressing several critical questions. “Is this neglect?” “Have the circumstances harmed the child, or jeopardized the child’s health and safety?” Suboptimal treatment adherence may lead to few or no clear consequences. Inadequacies in the care children receive naturally fall along a continuum, requiring a range of responses tailored to the individual situation. Legal considerations or CPS policies may discourage physicians from labeling many circumstances as neglect. Even if neglect does not meet a threshold for reporting to CPS, child healthcare professionals can still help ensure children’s needs are adequately met.

GENERAL PRINCIPLES FOR ASSESSING POSSIBLE ABUSE AND NEGLECT

The heterogeneity of circumstances in situations of child maltreatment precludes specific details. The following are useful general principles:

* Given the complexity and possible ramifications of determining child maltreatment, an interdisciplinary assessment is optimal, with input from all involved professionals. Consultation with a physician expert in child maltreatment is recommended.

Figure 40-9 Retinal hemorrhages. Arrows point to hemorrhages of various sizes.
A thorough history should be obtained from the parent(s) optimally via separate interviews.

Verbal children should be interviewed separately, in a developmentally appropriate manner. Open-ended questions (e.g., “Tell me what happened”) are best. Some children need more directed questioning (e.g., “How did you get that bruise?”); others need multiple choice questions. Leading questions (e.g., “Did your daddy hit you?”) must be avoided.

A thorough physical examination is necessary.

Careful documentation of the history and physical is essential. Verbatim quotes are valuable, including the question that prompted the response. Photographs are helpful.

For abuse: What is the evidence for concluding abuse? Have other diagnoses been ruled out? What is the likely mechanism of the injury? When did the injury likely occur?

For neglect: Do the circumstances indicate that the child’s needs have not been adequately met? Is there evidence of actual harm? Is there evidence of potential harm and on what basis? What is the nature of the neglect? Is there a pattern of neglect?

Are there indications of other forms of maltreatment? Has there been prior CPS involvement?

A child’s safety is a paramount concern. What is the risk of imminent harm, and of what severity?

What is contributing to the maltreatment? Consider the categories described in the section on etiology.

What strengths/resources are there? This is as important as identifying problems.

What interventions have been tried, with what results? Knowing the nature of these interventions can be useful, including from the parent’s perspective.

What is the prognosis? Is the family motivated to improve the circumstances and accept help, or resistant? Are suitable resources, formal and informal, available?

Are there other children in the home who should be assessed for maltreatment?

GENERAL PRINCIPLES FOR ADDRESSING CHILD MALTREATMENT

The circumstances surrounding each child and/or incident of suspected abuse or neglect may be complex and highly variable, precluding specific steps. The following are general principles.

• Treat any medical problems.
• Help ensure the child’s safety, often in conjunction with CPS; this is a priority.
• Convey concerns of maltreatment to parents, kindly but forthrightly. Avoid blaming. It is natural to feel anger or pain towards parents of maltreated children, but they need support and deserve respect.
• Have a means of addressing the difficult emotions child maltreatment can evoke in us.
• Be empathic and state interest in helping, or suggest another pediatrician.
• Know your national and state laws and/or local CPS policies on reporting child maltreatment. In the United States, the legal threshold for reporting is typically “reason to believe”; one does not need to be certain. Physical abuse and moderate to severe neglect warrant a report. In less-severe neglect, less-intrusive interventions may be an appropriate initial response. For example, if an infant’s mild failure to thrive is a result of an error in mixing the formula, parent education and perhaps a visiting nurse should be tried. In contrast, severe failure to thrive may require hospitalization, and if the contributing factors are particularly serious (e.g., a psychotic mother), out-of-home placement may be needed. CPS can assess the home environment, providing valuable insights.
• Reporting child maltreatment is never easy. Parental inadequacy or culpability is at least implicit, and parents may express considerable anger. Child healthcare professionals should supportively inform families directly of the report; it can be explained as an effort to clarify the situation and provide help, as well as a professional (and legal) responsibility. Explaining what the ensuing process is likely to entail (e.g., a visit from a CPS worker and sometimes a police officer) may ease a parent’s anxiety. Parents are frequently concerned that they might lose their child. Child healthcare professionals can cautiously reassure parents that CPS is responsible for helping children and families and that, in most instances, children remain with their parents. Even when CPS does not accept a report or when a report is not substantiated, they may offer voluntary supportive services such as food, shelter, homemaker services, and child care. Child healthcare professionals can be a useful liaison between the family and the public agencies, and should try to remain involved after reporting to CPS.
• Help address contributory factors, prioritizing those most important and amenable to being remedied. Concrete needs should not be overlooked; accessing nutrition programs, obtaining health insurance, enrolling children in preschool programs, and help finding safe housing can make a valuable difference. Parents may need their own problems addressed to enable them to adequately care for their children.
• Establish specific objectives (e.g., no hitting, diabetes will be adequately controlled), with measurable outcomes (e.g., urine dipsticks, hemoglobin A1c). Similarly, advice should be specific and limited to a few reasonable steps. A written contract can be very helpful.
• Engage the family in developing the plan, solicit their input and agreement.
• Build on strengths; there are always some. These provide a valuable way to engage parents.
• Encourage informal supports (e.g., family, friends; invite fathers to office visits). This is where most people get their support, not from professionals. Consider support available through a family’s religious affiliation.
• Consider children’s specific needs. Too often, maltreated children do not receive direct services.
• Be knowledgeable about community resources, and facilitate appropriate referrals.
• Provide support, follow-up, review of progress, and adjust the plan if needed.
• Recognize that maltreatment often requires long-term intervention with ongoing support and monitoring.

OUTCOMES OF CHILD MALTREATMENT

Child maltreatment often has significant short- and long-term medical, mental health, and social sequelae. Physically abused children are at risk for many problems, including conduct disorders, aggressive behavior, decreased cognitive functioning, and poor academic performance. Neglect is similarly associated with many potential problems. Even if a maltreated child appears to be functioning well, healthcare professionals and parents need to be sensitive to the possibility of later problems. Maltreatment is associated with increased risk in adulthood for several health risk behaviors and physical and mental health problems. Maltreated children are at risk for becoming abusive parents. The neurobiologic effects of child abuse and neglect on the developing brain may partly explain some of these sequelae.

Some children appear to be resilient and may not exhibit sequelae of maltreatment, perhaps owing to protective factors or interventions. The benefits of intervention have been found in even the most severely neglected children, such as those from Romanian orphans, who were adopted—the earlier the better.

PREVENTION OF CHILD ABUSE AND NEGLECT

An important aspect of prevention is that many of the efforts to strengthen families and support parents should promote children’s health, development, and safety, as well as prevent child abuse and neglect. Medical responses to child maltreatment have typically occurred after the fact; preventing the problem is preferable. Child healthcare professionals can help in several ways. An ongoing relationship offers opportunities to develop trust and knowledge of a family’s
circumstances. Astute observation of parent-child interactions can reveal useful information.

Parent and child education regarding medical conditions helps to ensure implementation of the treatment plan and to prevent neglect. Possible barriers to treatment should be addressed. Practical strategies such as writing down the plan can help. In addition, anticipatory guidance may help with child rearing, diminishing the risk of maltreatment. Hospital-based programs that educate parents about infant crying and the risks of shaking the infant may help prevent AHT. Screening for major psychosocial risk factors for maltreatment (depression, substance abuse, intimate partner violence, major stress), and helping address identified problems, often via referrals, may help prevent maltreatment. The primary care focus on prevention offers excellent opportunities to screen briefly for psychosocial problems. The traditional organ system-focused review of systems can be expanded to probe areas such as feelings about the child, the parent’s own functioning, possible depression, substance abuse, intimate partner violence, disciplinary approaches, stressors, and supports. The Safe Environment for Every Kid (SEEK) model offers a promising approach for pediatric primary care to identify and help address prevalent psychosocial problems. So doing can strengthen families, support parents, promote children's health, development and safety, and, help prevent child maltreatment.

Obtaining information directly from children or youth is also important, especially given that separate interviews with teens have become the norm. Any concerns identified on such screens require at least brief assessment and initial management, which may lead to a referral for further evaluation and treatment. More frequent office visits can be scheduled for support and counseling while monitoring the situation. Other key family members (e.g., fathers) might be invited to participate, thereby encouraging informal support. Practices might arrange parent groups through which problems and solutions are shared.

Advocacy
Child health professionals can assist in understanding what contributed to the child’s maltreatment. When advocating for the best interest of the child and family, addressing risk factors at the individual, family, and community levels is optimal. At the individual level, an example of advocating on behalf of a child is explaining to a parent that an active toddler is behaving normally and not intentionally challenging the parent. Encouraging a mother to seek help dealing with a violent spouse, saying for example, “You and your life are very important,” asking about substance abuse and helping parents obtain health insurance for their children are all forms of advocacy. Child abuse can and does occur even in families in which one spouse does not support or condone the abusive behavior (Fig. 40-10).

Efforts to improve family functioning, such as encouraging fathers’ involvement in child care are also examples of advocacy. Remaining involved after a report to CPS and helping ensure appropriate services are provided is advocacy as well. In the community, child health professionals can be influential advocates for maximizing resources devoted to children and families. These include parenting programs, services for abused women and children, and recreational facilities. Finally, child health professionals can play an important role in advocating for policies and programs at the local, state, and national levels to benefit children and families. Child maltreatment is a complex problem that has no easy solutions.

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40.1 Sexual Abuse

Wendy G. Lane and Howard Dubowitz

See also Chapter 119, Adolescent Rape.

Approximately 25% of girls and 10% of boys in the United States will be sexually abused at some point during their childhood. Rates vary across the globe, with children in some countries experiencing even higher rates. Whether children and families share this information with their pediatrician will depend, in large part, on the pediatrician's comfort with and openness to discussing possible sexual abuse with families.

Pediatricians may play a number of different roles in addressing sexual abuse, including identification, reporting to CPS, testing for and treating sexually transmitted infections, and providing support and reassurance to children and families. Pediatricians may also play a role in the prevention of sexual abuse by advising parents and children about ways to help keep safe from sexual abuse. In many jurisdictions throughout the United States, general pediatricians will play a triage role, with the definitive medical evaluation conducted by a child abuse specialist.

DEFINITION

Sexual abuse may be defined as any sexual behavior or action toward a child that is unwanted or exploitative. Some legal definitions distinguish sexual abuse from sexual assault; the former being committed by a caregiver or household member, and the latter being committed by someone with a noncustodial relationship or no relationship with the child. For this chapter, the term sexual abuse encompasses both abuse and assault. Sexual abuse does not have to involve direct touching or contact by the perpetrator. Showing pornography to a child, filming or photographing a child in sexually explicit poses, and encouraging or forcing one child to perform sex acts on another also constitute sexual abuse.

PRESENTATION OF SEXUAL ABUSE

Caregivers may become concerned about the possibility of sexual abuse when children exhibit sexually explicit behavior. This behavior includes that which is outside the norm for a child's age and developmental level. For preschool and school-age children, sexually explicit behavior may include compulsive masturbation, attempting to perform sex acts on adults or other children, or asking adults or children to perform sex acts on them. Teenagers may become sexually promiscuous and even engage in prostitution. Older children and teenagers may respond by sexually abusing younger children. It is important to recognize that this behavior could also result from accidental exposure (e.g., the child who enters his parent's bedroom at night to find his siblings having sex), or from neglect (e.g., watching pornographic movies where a child can see them).

Children who have been sexually abused sometimes provide a clear, spontaneous disclosure to a trusted adult. Often the signs of sexual abuse are much more subtle. For some children, behavioral changes are the first indication that something is amiss. Nonspecific symptoms include that which is outside the norm for a child's age and development. Regression in developmental milestones, including new-onset bedwetting or encopresis (see Chapter 23), is another behavior that caregivers may overlook as an indicator of sexual abuse. Teenagers may respond by becoming depressed, experimenting with drugs or alcohol, or running away from home. Because nonspecific symptoms are very common among children who have been sexually abused, it should nearly always be included in one's differential diagnosis of child behavior changes.

Some children may not exhibit behavioral changes or provide any other indication that something is wrong. For these children, sexual abuse may be discovered when another person witnesses the abuse or discovers evidence such as sexually explicit photographs or videos. Pregnancy may be another way that sexual abuse is identified. There are also children, with and without symptoms, who will not be identified at any point during their childhood.

THE ROLE OF THE GENERAL PEDIATRICIAN IN THE ASSESSMENT AND MANAGEMENT OF POSSIBLE SEXUAL ABUSE

Before determining where and how a child with suspected sexual abuse is evaluated, it is important to assess for and rule out any medical problems that can be confused with abuse. A number of genital findings may raise concern about abuse but often have alternative explanations. Genital redness in a prepubertal child is more often caused by nonspecific vulvovaginitis, eczema, or infection with staphylococcus, group A streptococcus, Neisseria, or yeast. Lichen sclerosis is a less-common cause of redness. Vaginal discharge can be caused by sexually transmitted infections, but also by vaginal foreign body, onset of puberty, or infection with Salmonella, Shigella, or Yersinia. Genital ulcers can be caused by herpes simplex virus and syphilis, but also by Epstein-Barr virus, varicella-zoster, Crohn disease, and Behçet disease. Genital bleeding can be caused by urethral prolapse, vaginal foreign body, accidental trauma, and vaginal tumor.

When other medical conditions are not under consideration, have been ruled out, or are less likely than abuse, the possibility for suspected sexual abuse should be probed (Fig. 40-11). Where and how a child with suspected sexual abuse is evaluated should be determined by how long ago the last incident of abuse likely occurred, and whether the child is prepubertal or postpubertal. For the prepubertal child, if abuse has occurred in the previous 72 hr, forensic evidence collection (e.g., external genital, vaginal, anal, and oral swabs, sometimes referred to as a "rape kit") is often indicated, and the child should be referred to a site equipped to collect forensic evidence. Depending on the jurisdiction, this site may be an emergency department, a child advocacy center, or an outpatient clinic. If the last incident of abuse occurred more than 72 hr prior, the likelihood of recovering forensic evidence is extremely low, and forensic evidence collection is not necessary. For postpubertal females, many experts recommend forensic evidence collection up to 120 hr following the abuse—the same time limit as for adult women. The extended time frame is justified because some studies have demonstrated that semen can remain in the postpubertal vaginal vault for more than 72 hr.

The referral site may be different when the child does not present until after the cutoff for an acute exam. Because emergency departments may not have a child abuse expert, and can be busy, noisy, and lacking in privacy, examination at an alternate location such as a child excess center, or an outpatient clinic. If the last incident of abuse occurred more than 72 hr prior, the likelihood of recovering forensic evidence is extremely low, and forensic evidence collection is not necessary. For postpubertal females, many experts recommend forensic evidence collection up to 120 hr following the abuse—the same time limit as for adult women. The extended time frame is justified because some studies have demonstrated that semen can remain in the postpubertal vaginal vault for more than 72 hr.

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advocacy center or outpatient clinic is recommended. If the exam is not urgent, waiting until the next morning is recommended because it is easier to interview and examine a child who is not tired and cranky. Referring physicians should be familiar with the triage procedures in their communities, including the referral sites for both acute and chronic exams, and whether there are separate referral sites for prepubertal and postpubertal children.

Children with suspected sexual abuse may present to the pediatrician's office with a clear disclosure of abuse or more subtle indicators. In this situation, a private, brief conversation between pediatrician and child can provide an opportunity for the child to speak in the child's own words without the parent speaking for the child. Doing this may be especially important when the caregiver does not believe the child, or is unwilling or unable to offer emotional support and protection. Telling caregivers that a private conversation is part of the routine assessment for the child's concerns can help comfort a hesitant parent.

When speaking with the child, experts recommend establishing rapport by starting with general and open-ended questions; for example: “Who lives at home?” and “What are your favorite things to do?” Questions about sexual abuse should be nonleading. A pediatrician should explain that sometimes children are hurt or bothered by others, and that the physician wonders whether that might have happened to the child. Open-ended questions, such as “Can you tell me more about that?” allow the child to provide additional information and clarification in the child's own words. It is not necessary to obtain extensive information about what happened because the child will usually have a forensic interview once a report is made to CPS and an investigation begins. Very young children and those with developmental delay may lack the verbal skills to describe what happened. In this situation, the caregiver's history may provide enough information to warrant a report to CPS without interviewing the child.

All 50 U.S. states (and a growing number of other nations) mandate that professionals report suspected maltreatment to CPS. The specific criteria for “reason to suspect” are generally not defined by state law. It is clear that reporting does not require certainty that abuse has occurred. Therefore, it may be appropriate to report a child with sexual behavior concerns when no accidental sexual exposure can be identified and the child does not clearly confirm or deny abuse during your conversation with her.

**PHYSICAL EXAMINATION OF THE CHILD WITH SUSPECTED SEXUAL ABUSE**

Many physicians are unfamiliar with genital anatomy and examination, particularly in the prepubertal child (Figs. 40-12 and 40-13). Because approximately 95% of children who undergo a medical evaluation following sexual abuse have normal exams, the role of the primary care provider is often simply to be able to distinguish a normal exam from findings indicative of common medical concerns or trauma. The absence of physical findings can often be explained by the type of sexual contact that has occurred. Abusive acts such as fondling or even

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**Figure 40-12 Female prepubertal genital anatomy.** A, Inset shows the region defined as the posterior hymenal rim, between the 4 o’clock and 8 o’clock positions (shaded blue). B, There is a range of normal anatomic variations in hymenal openings. Crescentic and annular are two of the most common shapes. C, Photographs illustrate the range of normal prepubertal and pubertal hymenal membranes. In most children, the hymen becomes thicker and more redundant during puberty. (From Berkoff MC, Zolotor AJ, Makoroff KL, et al: Has this prepubertal girl been sexually abused? JAMA 300:2779-2792, 2008.)
Abused Situations Involving a High Risk for abuse. In the acute time frame, lacerations or bruising of the labia, about the child’s physical health may allay fears and reduce anxiety for a small urethral prolapse, may be identified. In addition, reassurance or medical problems, such as labial adhesions, imperforate hymen, or abuse, and should not influence the decision to report to CPS. 

Even with the high proportion of normal genital exams, there is Evidence of genital, oral, or anal penetration or ejaculation. 

Table 40-5 Situations Involving a High Risk for Transmission of Sexually Transmitted Infections

| 1. Child has signs or symptoms of STI, including vaginal discharge or pain, genital itching or odor, urinary symptoms, and genital ulcers or lesions. |
| 2. The suspected perpetrator is known to have an STI, or is at high risk for having an STI because of multiple partners, substance abuse, or other reasons. |
| 3. Any other person living in the child’s household has an STI. |
| 4. There is evidence of genital, oral, or anal penetration or ejaculation. |
| 5. The patient or parent requests testing. |

STI, sexually transmitted infection. 


digital penetration can occur without causing injury. Many children do not disclose abuse until days, weeks, months, or even years after the abuse has occurred; because genital injuries can heal rapidly, injuries are often completely healed by the time a child presents for medical evaluation. A normal genital exam does not rule out the possibility of abuse, and should not influence the decision to report to CPS. 

Even with the high proportion of normal genital exams, there is value in conducting a thorough physical exam. Unsuspected injuries or medical problems, such as labial adhesions, imperforate hymen, or a small urethral prolapse, may be identified. In addition, reassurance about the child’s physical health may allay fears and reduce anxiety for the child and family. 

Few findings on the genital examination are diagnostic for sexual abuse. In the acute time frame, lacerations or bruising of the labia,
transmission. For both human papillomavirus and herpes simplex virus, the American Academy of Pediatrics recommends reporting to CPS unless perinatal or horizontal transmission is considered likely.

**SEXUAL ABUSE PREVENTION**

Pediatricians can play a role in the prevention of sexual abuse by educating parents and children about sexual safety at well child visits. During the genital exam the pediatrician can inform the child that only the doctor and select adult caregivers should be permitted to see their “private parts,” and that a trusted adult should be told if anyone else attempts to do so. Pediatricians can raise parental awareness that sometimes older kids or adults may try to engage in sexual behavior with children. The pediatrician can teach parents how to minimize limiting 1-adult/1-child situations and being sensitive to any adult’s unusual interest in young children. In addition, pediatricians can provide parents with suggestions about how to maintain open communication with their child that she or he was not at fault. Finally, pediatricians can provide parents with possible signs and symptoms, and how to reassure the child that she will be safe.

<table>
<thead>
<tr>
<th>ST/SA CONFIRMED</th>
<th>EVIDENCE FOR SEXUAL ABUSE</th>
<th>SUGGESTED ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonorrhea*</td>
<td>Diagnostic†</td>
<td>Report‡</td>
</tr>
<tr>
<td>Syphilis*</td>
<td>Diagnostic†</td>
<td>Report‡</td>
</tr>
<tr>
<td>HIV§</td>
<td>Diagnostic†</td>
<td>Report‡</td>
</tr>
<tr>
<td>Chlamydia trachomatis*</td>
<td>Diagnostic†</td>
<td>Report‡</td>
</tr>
<tr>
<td>Trichomonas vaginalis</td>
<td>Highly suspicious</td>
<td>Report‡</td>
</tr>
<tr>
<td>Condylomata acuminata</td>
<td>Suspicious</td>
<td>Report‡</td>
</tr>
<tr>
<td>Genital herpes*</td>
<td>Suspicious</td>
<td>Report‡</td>
</tr>
<tr>
<td>Bacterial vaginosis</td>
<td>Inconclusive</td>
<td>Medical follow-up</td>
</tr>
</tbody>
</table>

*Report if not likely to be perinatally acquired and rare nonsexual vertical transmission is excluded.
†Although culture is the gold standard, current studies are investigating the use of nucleic acid amplification tests as an alternative diagnostic method.
‡Report to the agency mandated to receive reports of suspected child abuse.
§Report unless a clear history of autoinoculation is evident.

**CLINICAL MANIFESTATIONS**

As with other forms of child abuse, the presentation of MCA may vary in nature and severity. Consideration of MCA should be triggered when the reported symptoms are repeatedly noted by only one parent, appropriate testing fails to confirm a diagnosis, and seemingly appropriate treatment is ineffective. The child’s symptoms, their course, or the response to treatment may be incompatible with any recognized disease. Preverbal children are usually involved, although older children may be convinced by parents that they have a particular problem and become dependent on the increased attention; this may lead to feigning symptoms.

Symptoms in young children are mostly associated with proximity of the offending caregiver to the child. The mother may present as a devoted or even model parent who forms close relationships with members of the healthcare team. While appearing very interested in her child’s condition, she may be relatively distant emotionally. She may have a history of Munchausen syndrome, though not necessarily diagnosed as such. Bleeding is a particularly common presentation. This may be caused by adding dyes to samples, adding blood (e.g., from the mother) to the child’s sample, or giving the child an anticoagulant (e.g., warfarin).

Seizures are a common manifestation, with a history easy to fabricate, and the difficulty of excluding the problem based on testing. A parent may report that another physician diagnosed seizures, and the myth may be continued if there is no effort to confirm the basis for the “diagnosis.” Alternatively, seizures may be induced by toxins, medications (e.g., insulin), water, or salts. Physicians need to be familiar with the substances available to families and the possible consequences of exposure.

Apnea is another common presentation. The observation may be falsified or created by partial suffocation. A history of a sibling with the same problem, perhaps dying from it, should be cause for concern. Parents of children hospitalized for apparent life-threatening events have been videotaped attempting to suffocate their child while in the hospital.

Gastrointestinal signs or symptoms are another common manifestation. Forced ingestion of medications such as ipecac may cause chronic vomiting, or laxatives may cause diarrhea.

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**Table 40-6** Implications of Commonly Encountered Sexually Transmitted (ST) or Sexually Associated (SA) Infections for Diagnosis and Reporting of Sexual Abuse Among Infants and Prepubertal Children

<table>
<thead>
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*Report if not likely to be perinatally acquired and rare nonsexual vertical transmission is excluded.
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‡Report to the agency mandated to receive reports of suspected child abuse.
§Report unless a clear history of autoinoculation is evident.

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**40.2 Medical Child Abuse (Fictitious Disorder by Proxy, Munchausen Syndrome by Proxy)**

Howard Dubowitz and Wendy G. Lane

The term Munchausen syndrome is used to describe situations in which adults falsify their own symptoms. In Munchausen syndrome by proxy, a parent, typically a mother, simulates or causes disease in her child. Several terms have been suggested to describe this phenomenon: factitious disorder by proxy, pediatric condition falsification, caregiver fabricated illness, and medical child abuse (MCA). In some instances, such as partial suffocation, “child abuse” may be most appropriate.

The core dynamic is that a parent falsely presents a child for medical attention. This may be via fabricating a history, such as reporting seizures that never occurred. A parent may directly cause a child’s illness by exposing a child to a toxin, medication, or infectious agent (e.g., injecting stool into an intravenous line). Signs or symptoms may also be manufactured, such as when a parent smother a child, or alters laboratory samples or temperature measurements. Each of these actions may lead to unnecessary medical care, sometimes including intrusive tests and surgeries. The “problems” often recur repeatedly over several years. In addition to the physical concomitants of testing and treatment, there are potentially serious and lasting social and psychologic sequelae.

Child health professionals are typically misled into thinking that the child really has a medical problem. Parents, sometimes working in a medical field, may be adept at constructing somewhat plausible presentations; a convincing seizure history may be offered, and a normal electroencephalogram cannot fully rule out the possibility of a seizure disorder. Even after extensive testing fails to lead to a diagnosis or treatment proves ineffective, health professionals may think they are confronting a “new or rare disease.” Unwittingly, this can lead to continued testing and interventions, thus perpetuating the MCA. Pediatricians generally rely on and trust parents to provide an accurate history. As with other forms of child maltreatment, accurate diagnosis of MCA requires that the pediatrician maintain a healthy skepticism under certain circumstances.

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**Bibliography is available at Expert Consult.**
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The skin, easily accessible, may be burned, dyed, tattooed, lacerated, or punctured to simulate acute or chronic skin conditions. Recurrent sepsis may be caused by infectious agents being administered; intravenous lines during hospitalization may provide a convenient portal. Urine and blood samples may be contaminated with foreign material, blood or stool.

DIAGNOSIS
In assessing possible MCA, several explanations should be considered in addition to a true medical problem. Some parents may be extremely anxious and genuinely concerned about possible problems. There may be many reasons underpinning this anxiety, such as a personality trait, the death of neighbor's child, or something read on the Internet. Alternatively, parents may believe something told to them by a trusted physician despite subsequent evidence to the contrary and efforts to correct the earlier misdiagnosis. Physicians may unwittingly contribute to a parent's belief that a real problem exists by, perhaps reasonably, persistently pursuing a medical diagnosis. There is a need to discern commonly used hyperbole (e.g., exaggerating the height of the fever) in order to evoke concern and perhaps justify a visit to an emergency department. In the end, a diagnosis of MCA rests on clear evidence of a child repeatedly being subjected to unnecessary medical tests and treatment, primarily stemming from a parent's actions. Determining the parent's underlying psychopathology is the responsibility of mental health professionals.

Once MCA is suspected, gathering and reviewing all the child's medical records is an onerous but critical first step. It is often important to confer with other treating physicians about what specifically was conveyed to the family. A mother may report that the child's physician insisted that a certain test be done when it may be the mother instead who demanded the test. It is also necessary to confirm the basis for a given diagnosis, rather than simply accepting a parent's account.

Pediatricians may face the dilemma of when to accept that all plausible diagnoses have been reasonably ruled out, the circumstances fit MCA, and further testing and treatment should cease. The likelihood of MCA must be balanced with concerns about possibly missing an important diagnosis. Consultation with a pediatrician expert in child abuse is recommended. In evaluating possible MCA, specimens should be carefully collected, with no opportunity for tampering with them. Similarly, temperature measurements should be closely observed.

Depending on the severity and complexity, hospitalization may be needed for careful observation to help make the diagnosis. In some instances, such as repeated apparent life-threatening events, covert video surveillance accompanied by close monitoring (to rapidly intervene in case a parent attempts to suffocate a child) can be valuable. It is important that there be close coordination among hospital staff, especially as some may side with the mother and resent even the possibility of MCA being raised. Parents should not be informed of the evaluation for MCA until the diagnosis is made. Doing so could naturally influence their behavior and jeopardize establishing the diagnosis. All steps in making the diagnosis and all pertinent information should be very carefully documented, perhaps using a “shadow” chart that the parent does not have access to.

TREATMENT
Once the diagnosis is established, the treatment plan should be worked out by the medical team and CPS; it may require out-of-home placement and should include mental healthcare for the offending parent as well as for older affected children. Further medical care should be carefully organized and coordinated by one primary care provider. CPS should be encouraged to meet with the family only after the medical team has informed the offending parent of the diagnosis; their earlier involvement may hamper the evaluation. Parents often respond with resistance, denial, and threats. It may be prudent to have hospital security in the vicinity.

Bibliography is available at Expert Consult.
Bibliography
Failure to thrive (FTT) results from inadequate usable calories necessary for a child’s metabolic and growth demands. No single set of growth parameters provides the criteria for a universal definition. FTT has classically been grouped into organic and nonorganic types; this construct is outmoded and not useful to clinicians seeking to address underlying causes, which are often multifactorial. Many would consider a weight for height ratio less than 2 SD (or <3 or 5 percentile) for age and gender diagnostic of FTT; others would use weight crossing 2 major percentiles on the growth curve. Patients with FTT may either have growth deceleration, faltering growth, or even weight loss.

A biopsychosocial model helps explain the complex interplay between even minor illnesses, the mental health of caregivers, and the home environment. The interaction between the child and parent is often complex; parent expectations of child behavior and the actual temperament of the infant create a transactional model where at times it is often difficult to separate cause and effect (action and reaction). The infant brings to this model an innate temperament with behavioral domains such as activity, adaptability, distractibility, response to new stimuli, and intensity of responses. Some infants are “easy babies,” whereas others are more “difficult.” These behaviors may interact with different maternal expectations or understanding of child behavior. Additional maternal contributions to this model may include postpartum depression, and the mother’s own history of abuse or neglect as a child, as well as home environmental issues such as family stress, poor social/emotional support, poverty, and a chaotic lifestyle. In addition, many medical causes of FTT are associated with these same psychosocial risk factors; both need to be addressed in the management of FTT.

**CLINICAL MANIFESTATIONS**

Inadequate weight for corrected age, weight for height, and body mass index, as well as failure to gain adequate weight over a period of time, help define FTT (see Chapter 15). Growth parameters should be measured serially and plotted on growth charts appropriate for the child’s sex, age, and, if preterm, postconceptual age. Growth charts are also available for some known chromosomal abnormalities, such as Down syndrome and Turner syndrome (see Chapter 81).

**ETIOLOGY AND DIAGNOSIS**

The causes of insufficient growth include (1) failure of the child to ingest and utilize sufficient calories, (2) malabsorption, and (3) increased metabolic demands. Focus the diagnostic approach on the cause of undernutrition. History, physical examination, and observation of the parent–child interaction in the clinical or home environment usually suggest the most likely etiologies and thus direct appropriate workup and management. A complete history should include a detailed nutritional, family, and prenatal history; documentation of child and caregiver interaction, the quantity, quality and frequency of meals, and further information regarding the onset of the growth failure (Table 41-1).

Many children with FTT will be solely categorized because of deprivation and/or psychological problems and rarely just because of child neglect. These families often share risk factors with neglect, such as poverty, social isolation, and caregiver mental health issues.

The medical causes of FTT may involve every organ system. The clinician may approach the diagnosis in terms of cause (Tables 41-2 and 41-3) or signs and symptoms (Table 41-4). The onset of growth deficiency can indicate a cause, such as the introduction of gluten into the diet of a child with celiac disease or a coincidental psychosocial event. A chromosomal abnormality, intrauterine infection, or
### Table 41-1
Historical Factors About the Period After the Neonatal Period to Be Considered in an Evaluation of Growth Failure Using a Biopsychosocial Model

<table>
<thead>
<tr>
<th>BIOLOGICAL SPHERE</th>
<th>PSYCHOSOCIAL SPHERES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency and source of routine medical care</td>
<td>Provision of baby care, especially feeding</td>
</tr>
<tr>
<td>Growth measurements</td>
<td>Maternal sleep deprivation</td>
</tr>
<tr>
<td>Immunization status</td>
<td>Postnatal depression or other mental illness</td>
</tr>
<tr>
<td>Medical illnesses</td>
<td>Type and amount of social support</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>Availability of respite for mother</td>
</tr>
<tr>
<td>Medications</td>
<td>Involvement of father and/or other intimate partner</td>
</tr>
<tr>
<td>Allergies—medications, food, other</td>
<td>Intimate partner violence</td>
</tr>
<tr>
<td>Surgeries</td>
<td>Financial resources, including money for baby supplies</td>
</tr>
<tr>
<td>Injuries, including bruises on infants</td>
<td>Enrollment in governmental aid programs</td>
</tr>
<tr>
<td>Feeding issues—vigorous or difficult feeder</td>
<td>Parental reaction to fussing/crying</td>
</tr>
<tr>
<td><strong>Breastfeeding:</strong></td>
<td>Who lives with baby</td>
</tr>
<tr>
<td>• Milk letdown</td>
<td>Reactions of others in the home to the baby</td>
</tr>
<tr>
<td>• Sense of fullness/emptying</td>
<td>Parental employment</td>
</tr>
<tr>
<td>• Frequency and duration of feedings</td>
<td>Use of daycare or babysitting</td>
</tr>
<tr>
<td>• Maternal observation of baby swallowing</td>
<td>Caregiver perception of weight gain and general appearance</td>
</tr>
<tr>
<td>• Maternal diet and medical problems while breastfeeding</td>
<td></td>
</tr>
<tr>
<td><strong>Formula feeding:</strong></td>
<td></td>
</tr>
<tr>
<td>• Type</td>
<td></td>
</tr>
<tr>
<td>• Method of mixing (concentration)</td>
<td></td>
</tr>
<tr>
<td>• Frequency and quantity of feedings</td>
<td></td>
</tr>
<tr>
<td>Other intake in first few months of life, such as:</td>
<td></td>
</tr>
<tr>
<td>• Water</td>
<td></td>
</tr>
<tr>
<td>• Juice</td>
<td></td>
</tr>
<tr>
<td>• Tea</td>
<td></td>
</tr>
<tr>
<td>• Soda</td>
<td></td>
</tr>
<tr>
<td>• Cereal</td>
<td></td>
</tr>
<tr>
<td>Sleep schedule</td>
<td></td>
</tr>
<tr>
<td>Baby’s temperament</td>
<td></td>
</tr>
<tr>
<td>Developmental milestones</td>
<td></td>
</tr>
<tr>
<td>Use of alternative or complementary medicines</td>
<td></td>
</tr>
</tbody>
</table>

**From Jenny C: Child abuse and neglect: diagnosis, treatment, and evidence, Philadelphia, 2011, Elsevier/Saunders, p. 554, Table 57-5.**

### Table 41-2
Diagnostic Classification of Causes and Selected Examples of Failure to Thrive

<table>
<thead>
<tr>
<th>INADEQUATE INTAKE</th>
<th>MALABSORPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inadequate food offered</strong></td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>• Food insecurity</td>
<td>Celiac disease</td>
</tr>
<tr>
<td>• Poor knowledge of child’s needs</td>
<td>Hepatobiliary disease</td>
</tr>
<tr>
<td>• Formula dilution or excessive juice</td>
<td>Food protein allergy, insensitivity, or intolerance</td>
</tr>
<tr>
<td>• Breastfeeding difficulties</td>
<td>Infection (giardiasis)</td>
</tr>
<tr>
<td>• Medical child abuse/caregiver fabricated illness (Munchausen by proxy)</td>
<td>Short gut syndrome</td>
</tr>
<tr>
<td>• Medical neglect</td>
<td></td>
</tr>
<tr>
<td>• Food fads including “rice” milk as substitute for formula or cow milk</td>
<td></td>
</tr>
<tr>
<td><strong>Child not taking enough food</strong></td>
<td><strong>INCREASED METABOLIC DEMAND</strong></td>
</tr>
<tr>
<td>• Oromotor dysfunction, neurologic disease</td>
<td>Insulin resistance (intrauterine growth restriction)</td>
</tr>
<tr>
<td>• Developmental delay</td>
<td>Congenital infections (human immunodeficiency virus, TORCHES)</td>
</tr>
<tr>
<td>• Behavioral feeding problem (altered oromotor sensitivity, pain and conditioned aversion)</td>
<td>Syndromes (Russell-Silver, Turner, Down)</td>
</tr>
<tr>
<td>• Anorexia from systemic causes</td>
<td>Malignancy</td>
</tr>
<tr>
<td><strong>Emesis</strong></td>
<td>Chronic disease (cardiac, pulmonary, renal)</td>
</tr>
<tr>
<td>• Pyloric stenosis</td>
<td>Metabolic disorders</td>
</tr>
<tr>
<td>• Gastroesophageal reflux</td>
<td>Immunodeficiency/autoinflammatory disorders</td>
</tr>
<tr>
<td>• Eosinophilic esophagitis</td>
<td>Endocrine (diabetes mellitus, diabetes insipidus, hyperthyroidism)</td>
</tr>
<tr>
<td>• Vascular rings</td>
<td></td>
</tr>
<tr>
<td>• Malrotation with intermittent volvulus</td>
<td></td>
</tr>
<tr>
<td>• Increased intracranial pressure and other neurologic disorders</td>
<td></td>
</tr>
<tr>
<td>• Inborn errors of metabolism</td>
<td></td>
</tr>
<tr>
<td>• Ruminating</td>
<td></td>
</tr>
<tr>
<td>• Cyclic vomiting</td>
<td></td>
</tr>
</tbody>
</table>

TORCHES, toxoplasma, other agents, rubella, cytomegalovirus, herpes simplex.

### Table 41-3

<table>
<thead>
<tr>
<th>Failure to Thrive: Differential Diagnosis by System</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSYCHOSOCIAL/BEHAVIORAL</strong></td>
</tr>
<tr>
<td>Inadequate diet because of poverty/food insufficiency, errors in food preparation</td>
</tr>
<tr>
<td>Poor parenting skills (lack of knowledge of sufficient diet)</td>
</tr>
<tr>
<td>Child/parent interaction problems (autonomy struggles, coercive feeding, maternal depression)</td>
</tr>
<tr>
<td>Food refusal</td>
</tr>
<tr>
<td>Rumination</td>
</tr>
<tr>
<td>Parental cognitive or mental health problems</td>
</tr>
<tr>
<td>Child abuse or neglect; emotional deprivation</td>
</tr>
<tr>
<td><strong>NEUROLOGIC</strong></td>
</tr>
<tr>
<td>Cerebral palsy</td>
</tr>
<tr>
<td>Hypothalamic and other central nervous system tumors (diencephalic syndrome)</td>
</tr>
<tr>
<td>Neuromuscular disorders</td>
</tr>
<tr>
<td>Neurodegenerative disorders</td>
</tr>
<tr>
<td><strong>RENAL</strong></td>
</tr>
<tr>
<td>Recurrent urinary tract infection</td>
</tr>
<tr>
<td>Renal tubular acidosis</td>
</tr>
<tr>
<td>Renal failure</td>
</tr>
<tr>
<td><strong>ENDOCRINE</strong></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Diabetes insipidus</td>
</tr>
<tr>
<td>Hypothyroidism/hyperthyroidism</td>
</tr>
<tr>
<td>Growth hormone deficiency</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
</tr>
<tr>
<td><strong>GENETIC/METABOLIC/CONGENITAL</strong></td>
</tr>
<tr>
<td>Sickle cell disease</td>
</tr>
<tr>
<td>Inborn errors of metabolism (organic acidosis, hyperammonemia, storage disease)</td>
</tr>
<tr>
<td>Fetal alcohol syndrome</td>
</tr>
<tr>
<td>Skeletal dysplasias</td>
</tr>
<tr>
<td>Chromosomal disorders</td>
</tr>
<tr>
<td>Multiple congenital anomaly syndromes (VATER, CHARGE)</td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL</strong></td>
</tr>
<tr>
<td>Pyloric stenosis</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
</tr>
<tr>
<td>Repair of tracheoesophageal fistula</td>
</tr>
<tr>
<td>Malrotation</td>
</tr>
<tr>
<td>Malabsorption syndromes</td>
</tr>
<tr>
<td>Celiac disease</td>
</tr>
<tr>
<td>Milk intolerance: lactose, protein</td>
</tr>
<tr>
<td>Pancreatic insufficiency syndromes (cystic fibrosis)</td>
</tr>
<tr>
<td>Chronic cholestasis</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Chronic congenital diarrhea states</td>
</tr>
<tr>
<td>Short bowel syndrome</td>
</tr>
<tr>
<td>Pseudooobstruction</td>
</tr>
<tr>
<td>Hirschsprung disease</td>
</tr>
<tr>
<td>Food allergy</td>
</tr>
<tr>
<td><strong>CARDIAC</strong></td>
</tr>
<tr>
<td>Cyanotic heart lesions</td>
</tr>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Vascular rings</td>
</tr>
<tr>
<td><strong>PULMONARY/RESPIRATORY</strong></td>
</tr>
<tr>
<td>Severe asthma</td>
</tr>
<tr>
<td>Cystic fibrosis; bronchiectasis</td>
</tr>
<tr>
<td>Chronic respiratory failure</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
</tr>
<tr>
<td>Adenoid/tonsillar hypertrophy</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
</tr>
<tr>
<td><strong>MISCELLANEOUS</strong></td>
</tr>
<tr>
<td>Collagen-vascular disease</td>
</tr>
<tr>
<td>Malignancy</td>
</tr>
<tr>
<td>Primary immunodeficiency</td>
</tr>
<tr>
<td>Transplantation</td>
</tr>
<tr>
<td><strong>INFECTIONS</strong></td>
</tr>
<tr>
<td>Perinatal infection (TORCHES)</td>
</tr>
<tr>
<td>Occult/chronic infections</td>
</tr>
<tr>
<td>Parasitic infestation</td>
</tr>
<tr>
<td>Tuberculosis</td>
</tr>
<tr>
<td>HIV</td>
</tr>
</tbody>
</table>

CHARGE, coloboma, heart disease, atresia choanae, retarded growth and retarded development and/or central nervous system anomalies, genital hypoplasia, and ear anomalies and/or deafness; TORCHES, toxoplasma, other agents, rubella, cytomegalovirus, herpes simplex; VATER, vertebral defects, imperforate anus, tracheoesophageal fistula, and radial and renal dysplasia.

### Table 41-4

<table>
<thead>
<tr>
<th>Approach to Failure to Thrive Based on Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HISTORY/PHYSICAL EXAMINATION</strong></td>
</tr>
<tr>
<td>Spitting, vomiting, food refusal</td>
</tr>
<tr>
<td>Diarrhea, fatty stools</td>
</tr>
<tr>
<td>Snoring, mouth breathing, enlarged tonsils</td>
</tr>
<tr>
<td>Recurrent wheezing, pulmonary infections</td>
</tr>
<tr>
<td>Recurrent infections</td>
</tr>
<tr>
<td>Travel to/from developing countries</td>
</tr>
<tr>
<td><strong>DIAGNOSTIC CONSIDERATION</strong></td>
</tr>
<tr>
<td>Gastroesophageal reflux, chronic tonsillitis, food allergies, eosinophilic esophagitis</td>
</tr>
<tr>
<td>Malabsorption, intestinal parasites, milk protein intolerance, pancreatic insufficiency, celiac disease, immunodeficiency, inflammatory bowel disease</td>
</tr>
<tr>
<td>Adenoid hypertrophy, obstructive sleep apnea</td>
</tr>
<tr>
<td>Asthma, aspiration, food allergy, cystic fibrosis, immunodeficiency</td>
</tr>
<tr>
<td>HIV or congenital immunodeficiency diseases, anatomic defects</td>
</tr>
<tr>
<td>Parasitic or bacterial infections of the gastrointestinal tract</td>
</tr>
</tbody>
</table>

Laboratory evaluation of children with FTT should be judicious and based on findings from the history and physical. Obtaining the state’s newborn screening results, a complete blood count, and urinalysis represent a reasonable initial screen. Testing for celiac disease is indicated in children if the poor growth coincided with gluten exposure (see Chapter 338).

**TREATMENT**

Treatment requires a multidisciplinary approach and an understanding of all the medical and psychosocial elements that contribute to a child’s growth failure since birth. Investigation for metabolic disorders should be considered in children with FTT accompanied by 1 of the following factors: history of acute, severe, and potentially life-threatening symptoms, recurrent vomiting, liver dysfunction, neurologic symptoms, cardiomyopathy and myopathy, impairment of special senses, renal symptoms, or distinct dysmorphic features and/or organomegaly.

The physical examination should focus on identifying chronic illnesses, recognizing syndromes that may alter growth, and documenting the effects of malnutrition (Table 41-5).
or purposeful neglect is a concern, the family should be referred to the child protective service team.

**PROGNOSIS**

FTT early in life, regardless of cause, is concerning because maximal postnatal brain growth occurs in the first 6 mo of life. Studies investigating the long-term sequelae of FTT in young infants and children have been conflicting, and there is no clear consensus regarding the long-term emotional, cognitive and metabolic effects. Despite inconclusive long-term outcomes in children who have FTT, investigators support early nutritional interventions for children who have poor growth. Early FTT may be associated with increased risk factors (including dyslipidemia, hypertension, and glucose intolerance) for cardiovascular disease as an adult perhaps relating to epigenetic responses to impaired nutrition and/or inflammation. The growing importance of cardiovascular disease among adults in lower and middle income nations where many children still have inadequate nutrition offers yet another reason why early FTT should be cause for concern globally.

Bibliography is available at Expert Consult.

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**Table 41-5**  
**Approach to Physical Examination**

<table>
<thead>
<tr>
<th>Vital signs</th>
<th>Blood pressure, if over 2 yr, temperature, pulse, respirations, oxygen saturation, anthropometry (growth percentiles, body mass index)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General appearance</td>
<td>Activity, affect, posture</td>
</tr>
<tr>
<td>Skin</td>
<td>Hygiene, rashes, trauma (bruises, burns, scars)</td>
</tr>
<tr>
<td>Head</td>
<td>Hair whorls, color and pluckability of hair, occipital alopecia, fontanel size and patency, frontal bossing, sutures, shape, facial dysmorphisms, philtrum</td>
</tr>
<tr>
<td>Eyes</td>
<td>Ptosis, strabismus, fundoscopic examination where possible, palpebral fissures, conjunctival pallor, icterus, cataracts</td>
</tr>
<tr>
<td>Ears</td>
<td>External form, rotation, tympanic membranes</td>
</tr>
<tr>
<td>Mouth, nose, throat</td>
<td>Thinness of lip, hydration, dental eruption and hygiene cares, glossitis, cheilosis, gum bleeding, marked tonsillar enlargement</td>
</tr>
<tr>
<td>Neck</td>
<td>Hairline, masses, lymphadenopathy</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Evidence of congestive heart failure, cyanosis</td>
</tr>
<tr>
<td>Abdomen</td>
<td>Protuberance, hepatosplenomegaly, masses</td>
</tr>
<tr>
<td>Genitalia</td>
<td>Malformations, hygiene, trauma</td>
</tr>
<tr>
<td>Rectum</td>
<td>Fissures, trauma, hemorrhoids</td>
</tr>
<tr>
<td>Extremities</td>
<td>Edema, dysmorphisms, rachitic changes, nails and nail beds</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Cranial nerves, reflexes, tone, retention of primitive reflexes, quality of voluntary movement</td>
</tr>
</tbody>
</table>


---

growth: a child’s health and nutritional status, family issues, and the parent–child interaction. An appropriate feeding atmosphere at home is important for all children with FTT.

Indications for hospitalization include severe malnutrition or failure of outpatient management. If a child requiring hospitalization has not responded after 2-3 mo of outpatient management, a specialized, multidisciplinary inpatient assessment should be considered. Inpatient care may include further diagnostic and laboratory evaluation, an assessment and implementation of adequate nutrition, and evaluation of the parent–child feeding interaction.

Children with severe malnutrition must be refeed carefully, with an incremental increase in calories to avoid refeeding syndrome (see Chapter 46). The type of caloric supplementation is based on the severity of FTT and the underlying medical condition. The response to feeding depends on the specific diagnosis, medical treatment, and severity of FTT. Minimal catch-up growth should generally be 2-3 times the average weight gain for corrected age. Multivitamin supplementation should be given to all children with FTT to meet the recommended dietary allowance, because these children commonly have iron, zinc, and vitamin D deficiencies, as well as increased micronutrient demands with catch-up growth.

Therapy for the psychosocial factors should be specific for the underlying issue (maternal depression, insufficient funds for food). In addition, parent education should focus on what is normal infant development and correcting any parental misconceptions about feeding and temperament, as well as learning the infant cues for hunger, satiety, and sleep. Some children who develop feeding aversion behaviors will require treatment by a specialized feeding team. If abuse
Bibliography


EPIDEMIOLOGY

Patterns of chronic illness in childhood are complex and dynamic. Serious chronic illness in children is less common than that among adults and widely heterogeneous. These differences have profound implications for the organization of children’s health services, as pediatricians have the difficult task of identifying and caring for children with unusual and varied conditions. Child health services have become far more reliant on standardized screening programs and formal systems of referral to regional specialty care programs than are healthcare systems for adults. Pediatrics has been characterized by rapid progress in preventing serious acute illnesses and extending the lives of children who previously would have succumbed to their illness early in life. These factors have made the epidemiology of childhood far more dynamic than that of the adult world.

National survey data suggest that 30% of all children have some form of chronic health condition (Table 42-1). If allergies, eczema, minor visual impairments, and other conditions not likely to generate serious consequences are excluded, then between 15% and 20% of all children have a chronic physical, learning, or developmental disorder. Boys have higher rates of chronic illness than do girls. There is considerable variation in the nature and severity of chronic illnesses in children (Table 42-2). The most common serious chronic condition is asthma, with 12% of children having received a diagnosis of asthma at some time in their lives; half of these children were reported to have experienced asthma symptoms in the prior 12 mo (see Chapter 144). Mental health and behavioral conditions represent a large and growing number of children with chronic illness. It has been estimated that almost 21% of U.S. children between 9 and 17 yr of age have a diagnosable mental or addictive disorder associated with some impairment; approximately 11% had significant impairment. Estimates suggest that 5% had major depression (see Chapter 26) and approximately 9.5% have attention-deficit/hyperactivity disorder (see Chapter 33). Overweight is not usually defined as a chronic health condition, but in 2013, the American Medical Association characterized obesity as a disease. In 2010 12% of 2-5 yr olds, 18% of 6-11 yr olds, and nearly 18% of all
These current prevalence figures represent a substantial increase in childhood chronic illness in the past several decades. In 2009, approximately 9% of children were reported to have a chronic health condition that limited their activities; the comparable figure in 1960 was only 2%. Although the increase in childhood chronic illness is likely partly a result of changes in survey methodologies, improvements in diagnosis, and expanded public awareness of behavioral and developmental disorders, there is strong evidence that the prevalence of certain important chronic child health conditions has increased. Asthma rates rose from 4% in 1980 to 9.5% in 2011, with the highest rates among the poorest children. The prevalence of attention-deficit/hyperactivity disorder and autism (see Chapter 30) has also increased considerably. Although improvements in the survival of infants and young children from prematurity, congenital anomalies, and genetic disorders have also

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**Table 42-1** Prevalence and Activity Limitation for Selected Chronic Diseases in Children <18 Yr of Age: United States, 2000-2003

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>NUMBER (IN THOUSANDS)</th>
<th>PREVALENCE (PER 100,000 CHILDREN)</th>
<th>ACTIVITY LIMITATION* (% OF CHILDREN WITH CONDITION)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>9,017</td>
<td>12,419</td>
<td>6.9</td>
</tr>
<tr>
<td>ADHD/ADD</td>
<td>4,034</td>
<td>6,078</td>
<td>5.5</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>2,061</td>
<td>3,145</td>
<td>16.7</td>
</tr>
<tr>
<td>Congenital and other heart conditions</td>
<td>957</td>
<td>1,318</td>
<td>9.76</td>
</tr>
<tr>
<td>Intellectual disability</td>
<td>447</td>
<td>677</td>
<td>27.7</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>273</td>
<td>375</td>
<td>36.24</td>
</tr>
<tr>
<td>Autism</td>
<td>234</td>
<td>322</td>
<td>18.2</td>
</tr>
<tr>
<td>Sickle cell anemia</td>
<td>151</td>
<td>209</td>
<td>23.91</td>
</tr>
<tr>
<td>Diabetes</td>
<td>120</td>
<td>166</td>
<td>4.8</td>
</tr>
<tr>
<td>Down syndrome</td>
<td>104</td>
<td>141</td>
<td>23.9</td>
</tr>
<tr>
<td>Arthritis</td>
<td>73</td>
<td>101</td>
<td>37.11</td>
</tr>
<tr>
<td>Muscular dystrophy</td>
<td>35</td>
<td>48</td>
<td>81.3</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>29</td>
<td>40</td>
<td>33.9</td>
</tr>
</tbody>
</table>

*Presence of an impairment or health problem that limits the ability to crawl, walk, run, or play. Figures based on weighted and age-adjusted national sample.

ADD, attention-deficit disorder; ADHD, attention-deficit/hyperactivity disorder.


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**Table 42-2** Quality Measures for Healthcare Received by Children with Special Healthcare Needs by Family Income: United States, 2005-2006 (Percent Meeting Quality Measure)

| MEDICAL PARTNERSHIP AND SATISFACTION WITH SERVICES* | MEDICAL HOME† | ADEQUATE INSURANCE‡ | EARLY AND CONTINUOUS SCREENING§ | COMMUNITY-BASED SERVICES|| | TRANSITION TO ADULT LIFE¶ |
|-----------------------------------------------------|---------------|---------------------|---------------------------------|----------------------------|---------------------------|--------------------------|
| <99% FPL                                             | 50.0          | 34.0                | 56.8                            | 47.7                       | 85.7                      | 24.3                     |
| 100-199% FPL                                        | 52.7          | 41.3                | 57.4                            | 56.9                       | 86.7                      | 33.7                     |
| 200-399% FPL                                        | 58.7          | 51.0                | 61.8                            | 66.8                       | 90.3                      | 43.5                     |
| >399% FPL                                           | 64.8          | 56.2                | 69.1                            | 76.8                       | 92.0                      | 53.7                     |

*Families of children and youth with special healthcare needs partner in decision-making at all levels and are satisfied with the services they receive.
†Children and youth with special healthcare needs receive coordinated ongoing comprehensive care within a medical home.
‡Families of children with special healthcare needs have adequate private and/or public insurance to pay for the services they need.
§Children are screened early and continuously for special healthcare needs.
||Community-based services for children and youth with special healthcare needs are organized so families can use them easily.
¶Youth with special healthcare needs receive the services necessary to make transitions to all aspects of adult life, including adult healthcare, work, and independence.

FPL, federal poverty line ($19,350 for family of 4 for the 48 contiguous states and the District of Columbia in 2005).


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children age 12 through 19 yr have a body mass index above the 95th percentile (see Chapter 47). Comorbid conditions, such as hypertension and a variety of metabolic disorders, may exist.

The severity and impact of chronic illnesses can vary significantly. Approximately 9% of all children have activity limitations as a consequence of 1 or more chronic illnesses, which has been relatively stable since 2001. Of these children, 40% have developmental or learning disorders, 35% have chronic physical conditions, and 25% report chronic mental health disorders. Approximately 2% of children have chronic conditions and activity limitation severe enough to meet eligibility criteria for the Supplemental Security Income program. Between 12% and 18% of all children meet the chronic illness and elevated service needs of the children with special healthcare needs (CSHCN) definition, depending on the data set that is examined.
contributed to the rising prevalence rates, this source accounts for only a small portion of all chronic illness in childhood.

Chronic illness accounts for a growing portion of child healthcare expenditures, serious illness, hospitalizations, and deaths among children in the United States. Across 37 children's hospitals, 19% of admission and 23% of inpatient charges were accounted for by only 3% of patients with frequent recurrent hospitalizations. Children with a chronic illness are hospitalized approximately 4 times more often and spend more than 7 times as many days in the hospital as children without a chronic illness. Estimates suggest that chronic illness accounts for the majority of all nontraumatic hospitalizations for children, a figure that has more than doubled in the past 4 decades, and children with chronic illnesses are experiencing increasing lengths of stay. Multiple admissions in any given year have also risen substantially: a child with a chronic condition is more likely to be readmitted, particularly for children with malignancies and neurologic conditions, although up to 25% of these may be planned admissions. The majority of all non–trauma-related deaths in children are now a result of chronic disorders. This historical shift in the distribution of pediatric hospitalization and mortality reflects not only the rise in the prevalence of childhood chronic illness, but also marked reductions in the incidence of serious acute pediatric illness.

Chronic illness is also contributing more profoundly to social disparities in child health. There are somewhat conflicting data on the association of poverty and the prevalence of chronic disorders in children, although most studies suggest a moderate elevation among poor children. Children enrolled in welfare cash assistance programs are more likely to have a chronic illness, and poor and African-American children have greater limitations in activity because of chronic conditions. Latino school-age children have rates of chronic illness that are similar to non-Latino whites; however, there remains little information on the prevalence and impact of chronic illness and its functional impact among the different subgroups of Latino children, as well as subgroups of Asian and Pacific Islanders.

ENHANCED NEEDS OF CHILDREN WITH CHRONIC ILLNESS AND THEIR FAMILIES

Although the nature and severity of chronic illness in children is quite heterogeneous, there are important clinical considerations that are common to virtually all such conditions regardless of their specific diagnosis or specialty group.

Financial Costs

The care required by children with serious chronic illnesses is usually associated with high financial costs. Even though the majority of children with chronic illness have coverage, 38% report being inadequately insured, experiencing gaps in coverage, and having costs or services not covered. Most states have some mechanism to facilitate health insurance coverage for children, although the nature and scope of these programs can vary considerably. A growing number of private and public health insurance plans require deductibles and copayments, which can accumulate rapidly for a child with a chronic illness. Some plans offer coverage up to a designated cost, period of hospitalization, or for a certain number of specialty visits. Once this cap has been reached, a larger portion or all of the costs may be borne by the family. This financial burden has been increasing over time, more so for families with private insurance: 20% of families have out-of-pocket expenses exceeding 10% of the family's income. The Family Opportunity Act of 2005 allows families of children with disabilities who are not financially eligible for Medicaid to buy into the program on a sliding scale. This program was created to fill the gap when children are underinsured because of private insurance limiting essential services, such as durable medical equipment and uncovered prescription drugs. The implementation of this program varies widely by state. The Patient Protection and Affordable Care Act, known colloquially as the ACA or "Obamacare," protects children with serious illness by instituting new insurance industry regulations, ending the practice of denying coverage to individuals with preexisting conditions, and allowing children to remain on their parents' insurance policies to the age of 26 yr.

Of great importance for children with serious chronic disorders, many new procedures, medications, and therapeutic regimens may be considered "experimental" by some insurers and not covered. Insurance coverage policies often generate strong incentives for hospital rather than outpatient care, even if the latter is indicated. Frequent medical visits and hospitalizations can interfere with parental employment and undermine job performance and security.

Complex Clinical Management

Children with serious chronic disorders usually require intense clinical management both in community and hospital settings. Close surveillance of disease progression, symptoms and functioning, and adverse medication effects often necessitate frequent communication and office visits. Managing hospital admissions and discharge planning may also prove complex and involve a variety of clinicians and community resources. As pressure to reduce hospitalization has grown, the burden on outpatient systems has increased accordingly. An uncoordinated approach to the multitude of required clinical visits can prove highly burdensome to the family and can undermine even the most committed family's attempts to comply. New models of care including accountable care organizations (ACOs) link care across the continuum, from quaternary to primary care by incentivizing multidisciplinary care teams to manage patients focusing on care coordination and prevention. The ability to capture savings through decreased admissions and emergency department use has been largely derived from the experiences of adult-focused programs; the feasibility and utility of pediatric ACOs, particularly for large populations of poor children, remain unexplored. The impact of ACOs and related financial arrangements on highly regionalized specialty service systems for children is of particular concern.

Pain

Many seriously ill children suffer from chronic pain (rheumatoid arthritis, spastic cerebral palsy), recurrent pain during exacerbations of underlying disease (inflammatory bowel diseases, sickle cell anemia), or acute pain related to procedures, surgeries, or diagnostic tests. This pain can alter a child's affect and influence their academic and social development, while also decreasing the family's quality of life (see Chapter 62). Assessing pain in young children or those with developmental disorders can be difficult and should always consider sociocultural and psychologic factors as well as developmental stage. Because serious, chronic pain is relatively unusual in children, its management may require the involvement of pediatric pain subspecialists who may practice with multidisciplinary teams in regional centers. The emotional toll on parents of children experiencing chronic pain can also be profound and require close attention by medical personnel.

Behavioral and Adjustment Issues

Although chronic illness in children elevates the likelihood that they will experience psychologic and behavioral problems, most children with chronic illness will experience the same level of psychologic and behavioral issues as other children their age. Behavioral and adjustment problems are more likely to occur the earlier the onset of the illness, particularly if it emerges in infancy. The risk of psychologic and behavioral problems does not appear to be associated with the severity of the chronic illness per se. These effects can occur across all diagnoses, although they are more profound for disorders that affect the central nervous system, including cerebral palsy, head trauma, and treatment-related complications that affect the brain, such as chemotherapy for cancer. Children with higher levels of cognitive ability appear to be less likely to develop serious behavioral or adjustment problems. Familial strife and mental illness, particularly depression in the mother, have been associated with an enhanced risk for psychologic and behavioral consequences.

Impact on Families

Like all children, a child with a chronic illness usually brings a mix of challenges and joy to a family. The presence of a chronic illness can add extra burdens, which can be expressed in a variety of forms. First,
the daily requirements of care should never be underestimated, particularly when the child is unable to perform tasks such as bathing, dressing, using the toilet, and feeding. Second, the care required by the child with chronic illness may divert needed attention from siblings and strain normal family dynamics. Third, the ultimate burden faced by families of children with a chronic illness is the emotional toll exacted by the daily struggles, pain, and, occasionally, early death that chronic illness can imply. Fourth, among the most difficult attributes of childhood chronic illness is the inherent unpredictability of its course and ultimate impact. Clinicians should be sensitive to how difficult it can be living with a child whose condition can worsen at any moment and without apparent cause. If conditions worsen to the point where medical care is futile, the evolving field of pediatric palliative care (see Chapter 43) can provide critical medical services and offer comprehensive support for grieving families. Fifth, children with serious chronic illness and their parents may harbor powerful hopes for new breakthroughs or divine intervention. Clinicians should understand the importance of these hopes for the families under their care and should explore related hopes for lesser, more incremental steps, such as attending school, playing sports, or taking a special trip.

Comprehensive Care and the Medical Home
All children require a clinician who takes responsibility for their comprehensive healthcare needs. To meet this responsibility, the coordinated implementation of a series of essential practice components, often termed the medical home, is recommended. These services should be provided within a broader system of care that emphasizes partnering in decision making between the family and medical providers, coordination of services among medical and community service providers, adequate health insurance coverage, ongoing screening for special healthcare needs, critical educational and community-based services, and special attention to the needs of older children as they transition to adult life and healthcare systems. Innovative new models are being suggested, including linkages between community health centers and academic medical partnerships, which combine the sub-specialist expertise, medical technology, and inpatient care of local academic medical centers with the primary care expertise of community health centers, to create a distinctive form of ACO. Evidence suggests that the extent to which these care requirements are being met for families with children with special healthcare needs is highly variable (see Table 42-1) and thus new models are needed. Although essential for all children, these practice elements take on special importance for children with chronic disorders and are outlined as follows.

Preventive Services
Primary, preventive care is an essential component of healthcare for children with chronic disease. Although overall CSHCN use preventive medical and dental services at rates similar to those of other children, primary preventive services can easily be overlooked in addressing the more specialized needs of these patients. The most common unmet healthcare need for CSHCN is dental care. Children with chronic disorders are commonly less-well immunized than their healthy counterparts. Well child care may be disrupted by visits for acute exacerbations of the chronic disorder and clinicians should carefully evaluate whether the chronic illness or its symptoms are contraindications to immunization. A family’s reliance on specialty services can be so great that the need for primary care services is overlooked. Special effort may be required to ensure the provision of high-quality primary care to children with chronic illness.

Continuity of Care
Children with chronic illnesses are particularly dependent on a stable, ongoing relationship with clinicians and the healthcare system. The duration and complexity of chronic illness in children require that the clinician responsible for coordinating the child's care have a good understanding of the child’s clinical history, including patterns of exacerbation and response to medications and other interventions. Continuity of care also serves as a basis for building trust and effective communication between affected families and clinicians, a prerequisite for high-quality care. Practice structures, therefore, should ensure the identification of a principal clinical provider and facilitate the provider's involvement in all necessary care. Transitioning of care as the child reaches adulthood is also critical, but is not experienced equally across the spectrum of medical need. The greatest difficulty in transitioning care occurs in youth with more complex conditions, those with cognitive impairments, and youth from racial/ethnic minority backgrounds. The transition requires planning, coordination and recognition of the emotional bonds that likely have developed between the child (and the child's family) and the practitioner (see Chapter 112.3).

Access to Urgent Care
Clinicians should expect that children with chronic illness will have enhanced requirements for urgent consultation, emergency care, and hospitalization. Practice mechanisms that ensure rapid access to medical consultation both by telephone and office visitation are essential. Procedures for urgent referral to appropriate facilities for emergency evaluation and hospitalization should also be established. This is particularly important in managed care systems that may require primary care referral or approval for care at referral sites.

Access to Specialty Care
Children with chronic illness commonly require specialized care. The need for specialty referral is particularly important in pediatrics because serious disorders are relatively rare in children. In many countries, including the United States, there is a shortage of many pediatric subspecialists. The ACA includes provisions to encourage pediatric residents to pursue pediatric subspecialty training. Regional systems of specialty referral and hospitalization have been formalized in the past several decades, particularly for perinatal care, pediatric trauma, and children with serious chronic illness. These systems of “regionalized” specialty care have been shown to reduce dramatically morbidity and mortality among affected children. It is crucial that policymakers who develop and implement health insurance products through new marketplaces or exchanges understand the need to include access to children’s hospitals and pediatric subspecialists for children with special healthcare needs. Pediatricians can play a crucial role in conveying to policymakers the special dependence of modern pediatrics on established regionalized systems of care. Regionalized care heavily relies on specialty care referrals, responsive communication between primary care practices and specialty programs is essential, particularly in conveying the reasons for referral, patient history, the nature and findings of the specialty evaluation, hospital course, and the collaborative development of a follow-up management plan.

Enhanced Information Systems
Children with chronic illness often require careful monitoring of their clinical status and the rapid evaluation of exacerbations. On-call and related coverage systems must include immediate access to up-to-date medical record information for children with complex histories and management regimens. Electronic medical records and systems that permit parent or other caretakers routine access to computerized medical record information may also prove useful. Access to current medical information, laboratory results, as well as clinical protocols and decision support algorithms could prove particularly helpful for children with complex healthcare requirements.

Linkage to Schools, Support Groups, and Community Services
Children with chronic illnesses often have special educational needs and may require the active participation of teachers and school health personnel in medical care plans. An important first step in creating a care plan is to assess the level of medical expertise available at the school site because many schools no longer have a nurse present. Special mechanisms should be established to ensure close coordination with schools, including provisions for collaborative evaluations of needs, monitoring of educational performance and social interactions, and the ongoing refinement of medical and educational management.
regimens. Clinicians can prevent the isolation many families feel by connecting them to support and advocacy groups composed of other parents with similarly affected children. Such connections have been facilitated by use of the Internet, which can link children and families over wide geographic areas.

**Logistic Access**
The difficulties that families can experience in transporting children with serious physical or behavioral disorders should never be underestimated. Particularly for older children or those requiring wheelchairs or other equipment, urban public transportation systems may be seriously impractical. In suburban and rural areas, transportation may involve traveling over great distances. For parents who have daytime employment, extended clinic hours may be required. Many communities have implemented innovative transportation programs for families in need of health and social services, particularly when available means of travel to clinical facilities is deemed unsafe or if it requires specially equipped vehicles or the assistance of trained personnel. In a growing number of areas, a variety of forms of telemedicine have enhanced access to medical and particularly, specialty care consultation.

**Cultural Sensitivity and Language Concordance**
See also Chapter 4.
Clinicians must possess a basic understanding of the meaning of illness and traditions of healing in the communities they serve. Cultural competency education is a required component of pediatric residency training, empowering a new generation of pediatricians with tools needed to bridge cultural divides. Although such cultural competence of individual providers is important, access also depends on creating clinical programs that respond to local perceptions and social institutions. Cultural competence not only reduces the likelihood of misunderstandings and medical errors, but also helps ensure that clinical programs can take full advantage of the many strengths that exist in culturally defined communities.

The most basic element of communication between clinicians and families of children with a chronic illness is that they share a common language. Clinicians should not overestimate their own or a parent's basic command of a language and must ensure that conveyed information is well understood. Children should not be used as interpreters despite the fact that they often have a better command of English than do their parents. Given the complex issues chronic illness can generate, it is far more useful to integrate trained interpreters into programs for chronically ill children in locations characterized by diverse language groups.

**Nondiscrimination in Access and Clinical Decision Making**
Clinicians who care for children with chronic illness must recognize the power of social status to define access to care. A history of inadequate service provision or different levels of service for distinct social groups can generate deep resentment and distrust for the medical system. **Family centered care**, defined in 1987 and incorporated into The Maternal and Child Health Bureau's core objectives, includes principles that build on family strengths, honor diversity, and emphasize the centrality of community-based services among others. Many studies have suggested that even when patients have adequate health insurance, poor and minority patients are less likely to be offered recommended diagnostic and therapeutic interventions. Although the precise reasons for these observations remain unclear, it is important that provider preconceptions do not replace a careful consideration of the true desires and capabilities of families, particularly in association with new, specialized, or home-based interventions. Strategies to confront these issues include implementing a family centered care approach training and recruitment of minority health providers, educational programs for clinicians, and the active assessment of clinical decision-making and family experiences at clinical facilities.

_Bibliography is available at Expert Consult._
Bibliography


The World Health Organization defines palliative care for children as “…the active total care of the child’s body, mind and spirit, and also involves giving support to the family…Optimally, this care begins when a life-threatening illness or condition is diagnosed and continues regardless of whether or not a child receives treatment directed at the underlying illness.” Provision of palliative care applies to children with a range of acute and chronic diseases, both life-threatening and life-altering, including, but not limited to, cancer, mitochondrial disorders, cardiac disease, neurodegenerative diseases, and trauma with life-threatening sequelae (Table 43-1). In fact, medical and technological advances have resulted in children living longer, often with significant dependence on new and complex technologies. These children have complex chronic conditions across the spectrum of congenital and acquired life-threatening disorders (see Chapter 42). Children with complex chronic conditions benefit from integration of palliative care strategies. These children, who often survive near-death crises followed by the renewed need for rehabilitative and life-prolonging treatments, are best served by a system that is flexible and responsive to changing needs.

<table>
<thead>
<tr>
<th>Table 43-1</th>
<th>Conditions Appropriate for Pediatric Palliative Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONDITIONS FOR WHICH CURATIVE TREATMENT IS POSSIBLE BUT MAY NOT SUCCEED</td>
<td>Advanced or progressive cancer or cancer with a poor prognosis Complex and severe congenital or acquired heart disease</td>
</tr>
<tr>
<td>CONDITIONS FOR WHICH THERE IS INTENSIVE LONG-TERM TREATMENT AIMED AT PROLONGING LIFE AND MAINTAINING QUALITY OF LIFE BUT PREMATURE DEATH IS STILL POSSIBLE</td>
<td>Human immunodeficiency virus infection Cystic fibrosis Severe immunodeficiency High-risk solid-organ transplant candidates and/or recipients such as lung or multivisceral Chronic or severe respiratory failure Muscular dystrophy Primary pulmonary hypertension</td>
</tr>
<tr>
<td>PROGRESSIVE CONDITIONS FOR WHICH THERE IS NO CURATIVE OPTION AND IN WHICH TREATMENT IS ALMOST EXCLUSIVELY PALLIATIVE AFTER DIAGNOSIS</td>
<td>Progressive metabolic disorders (e.g. mucopolysaccharidosis, Tay Sachs) Batten disease Severe forms of osteogenesis imperfecta</td>
</tr>
<tr>
<td>CONDITIONS INVOLVING SEVERE, NONPROGRESSIVE DISABILITY, CAUSING EXTREMELY VULNERABILITY TO HEALTH COMPLICATIONS</td>
<td>Severe cerebral palsy with recurrent infection or difficult-to-control symptoms Severe neurologic sequelae of infectious disease Hypoxic or anoxic brain injury Brain malformations such as holoprosencephaly or lissencephaly</td>
</tr>
</tbody>
</table>

Adapted from The Together for Short Lives (formerly the Association for Children’s Palliative Care [ACT]) Life-limiting/Life-threatening Condition Categories available at http://www.togetherforshortlives.org.uk/professionals/childrens_palliative_care_essentials/approach
Although palliative care is often mistakenly understood as equivalent to end-of-life care, its scope and potential benefit extend before and well after end-of-life and is applicable throughout the illness trajectory. Palliative care emphasizes optimization of quality of life, communication, and symptom control, aims that may be congruent with maximal treatment aimed at sustaining life.

The mandate of the pediatrician and other pediatric clinicians to attend to children's physical, mental, and emotional health and development includes the provision of palliative care for those children who live with a significant possibility of death before adulthood (Fig. 43-1). Such comprehensive physical, psychological, social, and spiritual care requires an interdisciplinary approach. This is often possible with creative use of professional hospital and community-based providers.

In the United States, the healthcare and reimbursement structure combined with frequent use of medical technology (e.g., home ventilatory support) or continuous home nursing historically precluded formal enrollment of children on the hospice benefit when they were otherwise eligible (i.e., had an estimated prognosis of 6 mo or less). Section 2302 of the Patient Protection and Affordable Care Act, termed the concurrent care for children requirement eliminated the requirement that Medicaid patients <21 yr of age forgo curative or life-prolonging therapies to be eligible for hospice. Although Medicaid programs in every state are now required to provide concurrent curative/life-prolonging treatment and hospice services for hospice-eligible children, development of systems to make such concurrent care a reality has been slow. A limitation of the concurrent care for children requirement is that it does not expand access to hospice for children with life-threatening illness who do not meet hospice eligibility criteria (i.e., have a prognosis that cannot be estimated to be <6 mo). A number of state-based pediatric palliative care coalitions have formed in recent years to improve access to home-based pediatric hospice/palliative care services, using strategies such as Medicaid waivers or state plan amendments to increase coverage for hospice services.

A growing number of home care agencies have also developed palliative care programs that serve as a bridge to hospice services for children not yet meeting hospice eligibility criteria. Provision of hospice or palliative care for children is often also limited by the availability of clinicians who have training or experience in caring for seriously ill children.

**CARE SETTINGS**

Pediatric palliative care should be provided across settings, including the hospital, outpatient settings, the home, pediatric nursing facilities, and inpatient hospice houses. **Home care** for the child with a life-threatening illness requires 24 hr per day access to experts in pediatric palliative care, a team approach, and an identified coordinator who serves as a link between hospitals, the community, and specialists and who may assist in preventing and/or arranging for hospital admissions, respite care, and increased home care support as needed. Adequate home care support and respite care, though very important, are often not readily available or families may feel using respite care is a personal failure, or they may worry that others cannot adequately care for their child’s special needs.

At the end of life, children and families may need intensive support. About half of pediatric deaths occur in acute-care hospitals, and end-of-life care may thus be provided in the home, hospital, pediatric nursing facility or hospice house. Families need to feel safe and well cared for and given permission, if possible, to choose location of care.

### Figure 43-1 Typical illness trajectories for children with life-threatening illness.

*From Field M, Behrman R, editors: When children die: improving palliative and end-of-life care for children and their families, Washington, DC, 2003, National Academies Press, p. 74, Fig. 3.1.*
PRIMARY AND SUBSPECIALTY PALLIATIVE CARE

Not all children with serious illness require care by a hospice and palliative medicine subspecialist or pediatric palliative care team. Basic palliative care knowledge, skills, and behaviors should be known to all clinicians who care for children with life-threatening illnesses and conditions. The role of the Hospice and Palliative Medicine subspecialist and team is to provide clinical consultation for more complex situations, to provide education and training, and to improve palliative care outcomes for all children and families through quality improvement and research.

COMMUNICATION, ADVANCE CARE PLANNING, AND ANTICIPATORY GUIDANCE

Although accurate prognostication is a particular challenge in pediatrics, the medical team often recognizes a terminal prognosis before the prognosis is understood by parents. This time delay may impede informed decision making about how the child lives at the end of life. Given the inherent prognostic uncertainty of a life-threatening diagnosis, discussions concerning resuscitation, symptom control, and end-of-life care planning should be initiated when the physician recognizes that a significant possibility of patient mortality exists. Having these conversations in the midst of a crisis is not ideal. Whenever possible, they should occur well in advance of the crisis or when the patient has recovered from a crisis, but is at high risk for others.

Patients and families are most comfortable being cared for by physicians and other care providers with whom they have an established relationship. Even in the face of long-standing and highly connected relationships, clinicians often hold assumptions about parent prognostic awareness, and parent readiness and willingness to have such discussions. In an attempt to protect families, clinicians may avoid conversations that they perceive as promoting hopelessness. However, parents greatly value honesty, and such conversations can promote parent hopefulness. A consultative palliative care team may provide the family with an opportunity to engage in sensitive conversations that are not as comfortably initiated with the primary team.

The population of children who die before reaching adulthood includes a disproportionate number of nonverbal and preverbal children who are developmentally unable to make autonomous care decisions. Although parents are usually the primary decision-makers, children should be as fully involved in discussions and decisions about their care as appropriate for their developmental status. Utilizing communication experts, child-life therapists, chaplains, social workers, psychologists, or psychiatrists to allow children to express themselves through art, play, music, talk, and writing will enhance the provider’s knowledge of the child’s understanding and hopes. Tools such as “Five Wishes” (for adults), “Voicing My Choices” (for adolescents), and “My Wishes” (for school-age children), have been useful in helping to gently introduce advance care planning to children, adolescents, and their families (http://www.agingwithdignity.org/index.php).

The Parents

From a parent’s perspective, compassionate communication with medical providers who understand their child’s illness, treatment options, and family beliefs and goals is the cornerstone of caring for children with life-threatening illness. During this period of time, one of the most significant relationships is that with the child’s pediatrician, who often has an enduring relationship with the child and family, including healthy siblings. Parents need to know that their child’s pediatrician will not abandon them as the goals of care evolve. A family’s goals may change with the child’s evolving clinical condition and other variable factors. A flexible approach rooted in ongoing communication and guidance that incorporates understanding of the family’s values, goals, and religious, cultural, spiritual, and personal beliefs is of paramount importance.

Pediatricians should recognize the important role they have in continuing to care for the child and family as the primary goal of treatment may simultaneously be prolongation of life and comfort, relief of suffering, and promoting quality of life. Regular meetings between caregivers and the family are essential in order to reassess and manage symptoms, explore the impact of illness on immediate family members, and provide anticipatory guidance. At these meetings, important issues with lifelong implications for parents and their child may be discussed. Such discussions should be planned with care, ensuring that adequate time for in-depth conversation is allotted; a private, physical setting is arranged; devices silenced; and that both parents and/or others who might be identified by the family as primary supports are present. Strategies for facilitating conversations related to goals of care and decision-making are detailed below.

Families may look to their pediatrician for assurance that all treatment options have been explored. Assisting a patient’s family to arrange a second opinion may be helpful. Listening to families and children speak about the future even in the face of poor prognosis may help keep the focus on living even while the child may be dying. Hoping for a miracle can coexist for parents even as they are facing and accepting the more likely reality of death.

Parents also need to know about the availability of home care, respite services, web-based support educational materials other media, and support groups. Responding to parent requests or need for counseling referrals for themselves, other children, or family is essential. Attending to the concrete needs of families such as financial, insurance and housing needs can be paramount in freeing them of worries that might interfere or compete with their ability to be fully present in their child’s care.

When closer to end of life, while broaching the topic may seem daunting, exploration of how parents envision their child’s death, addressing their previous loss experiences (most often with death of an adult relative) and any misconceptions they may have, is often a great relief to parents. Learning about cultural, spiritual, and family values regarding pain management, suffering, and the preferred place of end-of-life care is essential before death. Even raising thoughts about funeral arrangements, the possibility of autopsy, and organ/tissue donation can be helpful to give parents choices and know that these considerations can be discussed without fear.

A major worry of many parents is in how to involve and communicate with siblings as well as the child about the fact that most likely death is going to occur. Evidence shows that parents who have open conversations with their child about death and dying do not regret having done so. Clear communication around end-of-life issues, delivered with sensitivity and caring are directly correlated with ratings of high satisfaction with physician care. Such communication includes speaking directly to the child when appropriate. Communication is complicated by an assumed need for mutual protection in which the child wants to protect his or her parents and likewise the parents want to protect their child from painful information or sadness. Honoring the uniqueness of the child as well as understanding and respecting the family’s communication style, values, spirituality, and culture, is critical in these highly sensitive conversations.

In communications with the child and family, the physician should avoid giving specific estimates of survival length, even when the child or family explicitly asks for them. These predictions are invariably inaccurate because population-based statistics do not predict the course for individual patients. A more honest approach may be to explore ranges of time in general terms (“weeks to months,” “months to years”). The physician can also ask parents what they might do differently if they knew how long their child would live and then assist them in thinking through the options relating to their specific concerns (suggest celebrating upcoming holidays/important events earlier in order to take advantage of times when the child may be feeling better). It is generally wise to suggest that relatives who wish to visit might do so earlier rather than later, given the unpredictable trajectory of many conditions.

For the child and family, the integration of bad news is a process, not an event, and when done sensitively does not take away hope or alter the relationship between the family and physician. The physician should expect that some issues previously discussed may not be fully resolved for the child and parents (do-not-resuscitate [DNR] orders, artificial nutrition or hydration) and may need to be revisited over
time. Parents of a child with chronic illness may reject the reality of an impending death because past predictions may not have been accurate. Whether they are parents of a child with a chronic illness or of a child whose death is the result of accident or sudden catastrophic illness, they may experience great anxiety, guilt, or despair.

**The Child**

Truthful communication that takes into account the child’s developmental stage and unique lived experience can help to address the fear and anxiety commonly experienced among children with life-threatening illness. Responding in a developmentally appropriate fashion (Table 43-2) to a child’s questions about death, such as “What’s happening to me?” or “Am I dying?” requires a careful exploration of what is already known by the child, what is really being asked (the question behind the question), and why the question is being asked at this particular time and in this setting. It may signal a need to be with someone who is comfortable listening to such unanswerable questions. Many children find nonverbal expression much easier than talking; art, play therapy, and storytelling may be more helpful than direct conversation.

A child’s perception of death depends on the child’s conceptual understanding of *universal*ity (that all things inevitably die), *irreversibility* (that dead people cannot come back to life), *nonfunction*ality (that being dead means that all biologic functions cease), and *causality* (that there are objective causes of death). Very young children may struggle with the concepts of irreversibility and nonfunctionality. For young, school-age children, who are beginning to understand the finality of death, worries may include magical thinking in which their thoughts, wishes, or bad behavior might be the underlying cause for their illness. Older children seek more factual information to gain some control over the situation.

<table>
<thead>
<tr>
<th><strong>Table 43-2</strong></th>
<th>Developmental Questions, Thoughts, and Concepts of Dying and with Responsive Strategies</th>
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<tbody>
<tr>
<td><strong>TYPICAL QUESTIONS AND STATEMENTS ABOUT DYING</strong></td>
<td><strong>THOUGHTS THAT GUIDE BEHAVIOR</strong></td>
</tr>
<tr>
<td><strong>MOMTHS-3 YR</strong></td>
<td>“Mommy, don’t cry.” “Daddy, will you still tickle me when I’m dead?”</td>
</tr>
<tr>
<td><strong>3-5 YR</strong></td>
<td>“I did something bad and so I will die.” “Can I eat anything I want in heaven?”</td>
</tr>
<tr>
<td><strong>5-10 YR</strong></td>
<td>“How will I die?” “Will it hurt?” “Is dying scary?”</td>
</tr>
<tr>
<td><strong>10-18 YR</strong></td>
<td>“I’m afraid if I die my mom will just break down.” “I’m too young to die. I want to get married and have children.” “Why is God letting this happen?”</td>
</tr>
</tbody>
</table>

Children’s fears of death are often centered on the concrete fear of being separated from parents and other loved ones and what will happen to their parents rather than themselves. This can be true for teens and young adults as well. This fear may be responded to in different ways: some families may give reassurance that loving relatives will be waiting, while others use religious figures to refer to an eternal spiritual connection.

Even though adolescents may have a conceptual understanding of death similar to that of adults, working with the adolescent with life-threatening illness presents unique concerns and issues. The developmental work of adolescence includes separating from their parents, developing strong peer relationships, and moving towards independent adulthood. For this particular population, the teenager’s developmental need to separate is complicated by the often increasing dependence both physically and emotionally on the teenager’s parents. At the same time, adolescents are often asked to be part of the decision-making process without always having the emotional experience to fully understand the impact.

In addition to developmental considerations, understanding related to the child’s life experiences, the length of the child’s illness, the understanding of the nature and prognosis of the illness, the child’s role in the family (peacemaker, clown, troublemaker, the “good” child) should be considered in communication with children.

Parents have an instinctive and strong desire to protect their children from harm. When facing the death of their child, many parents attempt to keep the reality of impending death hidden from their child with the hope that the child can be “protected” from the harsh reality. Although it is important to respect parental wishes, it is also true that most children already have a sense of what is happening to their bodies even when it has been purposely left unspoken. Children may blame themselves for their illness and the hardships that it causes for their loved ones. Perpetuating the myth that “everything is going to be all right” takes away the chance to explore fears and provide reassurance. Honest communication also allows opportunities for memory and legacy making and saying goodbye.

School is the “work” of childhood and is important in optimizing quality of life for a child seeking “normalcy” in the face of illness. Finding ways to help children and their families to maintain these connections through modification of the school day and exploring options to promote educational and social connections into the home or into the hospital room can be meaningful in the event that a child is not well enough to attend school. Video conferencing can readily be arranged from almost any setting. As with the younger child, finding ways to help the adolescent maintain peer relationships and school based programming can be important in maximizing quality of life.

The Siblings

Brothers and sisters are at special risk both during their sibling’s illness and after the death. Because of the extraordinary demands placed on parents to meet the needs of their ill child and their own needs, healthy siblings may feel that their own needs are not being acknowledged or fulfilled. These feelings of neglect may then trigger guilt about their own good health and resentment toward their parents and ill sibling. Younger siblings may react to the stress by becoming seemingly oblivious to the turmoil around them. Some younger siblings may feel guilty as a result of “wishing” the affected child would die so they could get their parents back; preschool children may believe that their wishes caused the death of their sibling (“magical thinking”; see Chapter 7). Parents need to know that these are normal responses, and siblings should be encouraged to maintain the typical routines of daily living. Siblings who are most involved with their sick brothers or sisters before death usually adjust better both at the time of and after the death. Acknowledging and validating sibling feelings, being honest and open, and appropriately involving them in the life of their sick sibling provide a good foundation for the grief process. It is often helpful to identify a person in the family (such as a loving aunt) or school (such as a counselor) to offer confidential and supportive opportunities for the sibling to reflect on their family experience.

The Staff

Adequate support for the staff providing palliative care is necessary to prevent depression, emotional withdrawal, and/or other symptoms. Offering educational opportunities and emotional support for staff at various stages of caring for a child with life-threatening illness can be helpful in bettering patient/family care and preventing staff from experiencing compassion fatigue, burn out and long-term repercussions, including the possibility of leaving the field.

Goals of Care and Decision Making

In the course of a child’s life-limiting illness, a series of important decisions may arise in relation to location of care, medications with risks and benefits, not starting and or discontinuing life-prolonging treatments, experimental treatments in research protocols, and the use of integrative therapies (see Chapters 3 and 64). Such family decisions are greatly facilitated by opportunities for in-depth and guided discussions around goals of care for their child. This is often accomplished by eliciting parent (and child) understanding of the child’s condition and asking open-ended questions that explore the parent’s and child’s hopes, worries, and family values. Goals of care conversations include what is most important for them as a family, considerations of their child’s clinical condition, and their values and beliefs, including cultural, religious, and spiritual considerations. Table 43-3 lists specific questions that can effectively guide these discussions. The conversation should also include a review of previous discussions, active listening to concerns and issues as they are raised, opportunities to repeat back elements of the discussion to ensure clarity, and provision of honest, factual answers even in areas of uncertainty.

**Table 43-3**

<table>
<thead>
<tr>
<th>Five Basic Questions to Guide Goals of Care Conversation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tell us about your child as a person; what does your child enjoy?</td>
</tr>
<tr>
<td>What is your understanding of your child’s illness/condition?</td>
</tr>
<tr>
<td>In light of your understanding, what is most important to you regarding your child’s care?</td>
</tr>
<tr>
<td>What are you hoping for? What are your worries?</td>
</tr>
<tr>
<td>In the face of your child’s illness/condition, what gives you strength?</td>
</tr>
</tbody>
</table>

Resuscitation Status

The legal mandate requiring attempted resuscitation for cardiopulmonary arrest unless a written DNR order is in place is a complex and confusing concept for many parents. In broaching this topic, rather than asking parents if they want to forgo cardiopulmonary resuscitation for their child (and placing the full burden of decision making on them), it is preferable to discuss whether or not resuscitative interventions are likely to benefit the child. It is important to make recommendations based on overall goals of care and medical knowledge of potential benefit and/or harm of these interventions. Once the goals of therapy are agreed upon, the physician is required to write a formal order. Out-of-hospital DNR verification forms are available in many states, which, if completed on behalf of the child, affirm that rather than initiating resuscitative efforts, emergency response teams are obligated to provide comfort measures when called to the scene. Some states have implemented the **physician orders for life-sustaining treatment (POLST)** system. A POLST order is completed for children with life-threatening illness, translating the expressed wishes of the parents (and
in some cases, of the child) into actionable orders (www.polst.org). It may also be beneficial to write a letter delineating decisions regarding resuscitation interventions and supportive care measures to be undertaken for the child, particularly if POLST are not available. The letter should be as detailed as possible, including recommendations for comfort medications and contact information for caregivers best known to the patient. Such a letter, given to the parents, with copies to involved caregivers and institutions, can be a useful communication aid, especially in times of crisis. If a child may die in the home setting, and the parents opt to use on out-of-hospital DNR verification form or POLST, plans to pronounce the child and provide support for the family must be in place. If the child has been referred to hospice, the hospice personnel usually fulfill those responsibilities.

Conflicts in decision making can occur within families, within healthcare teams, between the child and family, and between the family and professional caregivers. For children who are developmentally unable to provide guidance in decision making (neonates, very young children, or children with cognitive impairment), parents and healthcare professionals may come to different conclusions as to what is in the child’s best interests. Given the shifting boundary that separates childhood from adulthood, decision making around the care of adolescents presents specific challenges. In some families and cultures, truth telling and autonomy are secondary to maintaining the integrity of the family. (see Chapter 4). Although frequently encountered, differences in opinion are often manageable for all involved when lines of communication are kept open, team and family meetings are held, and the goals of care are clear.

**Symptom Management**

Intensive symptom management is another cornerstone of pediatric palliative care. Alleviation of symptoms reduces suffering of the child and family, and allows them to focus on other concerns and participate in meaningful experiences. Despite increasing attention to symptoms, and pharmacologic and technical advances in medicine, children often suffer from multiple symptoms. Table 43-4 lists key elements and general approaches to managing symptoms.

**Pain** is a complex sensation triggered by actual or potential tissue damage and influenced by cognitive, behavioral, emotional, social, and cultural factors. Effective pain relief is essential to prevent central sensitization, a central hyperexcitation response that may lead to escalating pain, and to diminish a stress response that may have a variety of physiologic effects. Assessment tools include self-report tools for children who are able to communicate their pain verbally, as well as tools based on behavioral cues for children who are unable to do so because of developmental delays, medical conditions or cognitive limitations. Tables 43-5 to 43-7 address management of pain (see Chapter 62).

**Table 43-4** Key Elements of Effective Symptom Management

- Establish and periodically revisit goals of care and ensure that goals are communicated to entire care team.
- Anticipate and plan for symptoms before they occur.
- Assess the child for symptoms regularly, using consistent and developmentally appropriate assessment tools.
- Utilize self-report, if the child is able to reliably report symptoms.
- Evaluate all aspects of the symptom, including quality, frequency, duration, and intensity.
- Consider the holistic nature of symptoms.
- Explore the meaning that symptoms may have for families in their social, cultural, religious context.
- Assess distress caused by the symptom.
- Evaluate the degree of functional impairment from the symptom.
- Understand the pathophysiology of the symptom and establish a complete differential diagnosis.
- Treat the underlying cause if possible, weighing benefits and risks, in the context of goals of care.
- Choose the least-invasive route for medications—by mouth whenever possible.
- Prescribe regular medications for constant symptoms, and consider prn doses for breakthrough or uncontrolled symptoms.
- Consider both pharmacologic and nonpharmacologic approaches.
- Reassess the symptom and response to interventions regularly.
- For refractory symptoms, revisit the differential diagnosis and review potentially contributing factors.
- Effective interventions relieve the symptom and reduce distress and functional impairment.
- Partner with families to identify and address any barriers to optimal control of symptoms.
- Address spiritual, emotional, and existential suffering in addition to physical suffering as these are often interrelated.

**Table 43-5** Guidelines for Pain Management

- Utilize nonopioid analgesics as monotherapy for mild pain and together with opioids for more severe pain.
- Nonopioid analgesics include acetaminophen, nonsteroidal antiinflammatory drugs (NSAIDs), salicylates, and selective cyclooxygenase (COX-2) inhibitors.
- For moderate or severe pain, start with a short-acting opioid at regular intervals.
- When dose requirements have stabilized, consider converting opioid to a long-acting formulation with doses available for breakthrough or uncontrolled pain, as needed.
- For uncontrolled pain, increase opioid dose by 30-50%; for severe pain increase by 50-100%.
- Avoid codeine and opioids with mixed agonist activity (e.g., butorphanol, pentazocine).
- Administer medications via the simplest, most effective, and least-distressing route.
- Dispel the myth that strong medications should be saved for extreme situations or the very end of life.
- Opioids do not have a “ceiling effect,” and escalating symptoms may be treated with an increase in dose.
- Clarify for families the differences between tolerance, physical dependence, and addiction.
- Anticipate and treat/prevent common analgesic side effects (gastritis with NSAIDs; constipation, pruritus, nausea, sedation with opioids).
- Always initiate a bowel regimen to prevent constipation when starting opioids.
- Consider a stimulant for opioid-induced somnolence.
- Pruritus rarely indicates a true allergy. If not responsive to an antihistamine, consider low-dose naltrexone or switching opioids.
- Consider switching to a different opioid for intolerable side effects or neurotoxicity (e.g., myoclonus).
- Use an equianalgesic conversion table when switching opioids, and account for incomplete cross-tolerance.
- Consider the use of adjuvant drugs for specific pain syndromes, and for their opioid-sparing effect:
  - Antidepressants (e.g., amitriptyline, nortriptyline) and anticonvulsants (e.g., gabapentin, carbamazepine, topiramate) for neuropathic pain.
  - Steroids or NSAIDs for bone pain.
  - Sedatives and hypnotics for anxiety and muscle spasm.
  - To enhance analgesia from opioids, consider clonidine or ketamine.
  - Use topical local anesthetics (lidocaine, prilocaine, bupivacaine) when possible.
  - Consider anesthetic blocks for regional pain.
  - Consider palliative radiation therapy.
  - Consider psychological approaches (e.g., cognitive or behavioral therapy) and integrative therapies (e.g., acupuncture, massage).
<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>MEDICATION</th>
<th>STARTING DOSE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain—mild</td>
<td>Acetaminophen</td>
<td>15 mg/kg po q 4 hr, max 4 g/day</td>
<td>Available po (including liquid), pr, IV PO (including liquid) only; avoid if risk of bleeding; use only in infants 26 mo. Use with caution in congestive heart failure. Chewable tablets contain phenylalanine</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen</td>
<td>10 mg/kg po q 4 hr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trilisate</td>
<td>10-15 mg/kg po tid</td>
<td>Trilisate may have less antiplatelet activity and therefore pose less risk for bleeding than other salicylates. Salicylates, however, have been associated with Reye syndrome in children &lt;2 yr</td>
</tr>
<tr>
<td>Pain—moderate/severe</td>
<td>Morphine immediate release (i.e., MSIR)</td>
<td>0.3 mg/kg po q 4 hr if &lt;50 kg; 5-10 mg po q 4 hr††</td>
<td>Also available in IV/SQ formulation††</td>
</tr>
<tr>
<td></td>
<td>Oxycodeone</td>
<td>0.1 mg/kg po q 4 hr if &lt;50 kg; 5-10 mg po q 4 hr if &gt;50 kg††</td>
<td>No injectable formulation††</td>
</tr>
<tr>
<td></td>
<td>Hydromorphone</td>
<td>0.05 mg/kg po q 4 hr if &lt;50 kg; 1-2 mg po q 4 hr if &gt;50 kg††</td>
<td>Also available in IV/SQ formulation. Injectable form very concentrated, facilitating subcutaneous delivery‡§ Rapid infusion may cause chest wall rigidity‡§ Only opioid with immediate and prolonged effect available as a liquid; do not adjust dose more often than every 72 hr as prolonged biologic half-life &gt; than therapeutic half-life. Knowledge of the pharmacokinetics of methadone is needed for converting to and from doses of other opioids. Also available IV/SQ. May cause QT interval prolongation (consider ECG), especially in adults &gt;200 mg/day or in those at risk for QT prolongation. Interacts with several antiretrovirals†</td>
</tr>
<tr>
<td>Pain—sustained release</td>
<td>MS Contin Kadian (contains sustained-release pellets), Avinza (contains immediate and extended release beads) Oramorph OxyContin Transdermal fentanyl patch</td>
<td>Total daily dose of MSIR divided bid-tid</td>
<td>Do not crush MS Contin. For those unable to swallow pills, Kadian and Avinza capsules may be opened and contents mixed with food but cannot be chewed. Kadian contents may be mixed in 10 mL water and given via 16-French G-tube. Avoid alcohol with Avinza. Larger dose formulation may not be suitable for small children§</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total daily dose of oxycodeone divided bid-tid Divide 24-hr po morphine dose by 2 to determine starting dose of transdermal fentanyl. There is no data on the equianalgesic conversion from transdermal fentanyl to any oral opioid</td>
<td>Do not crush§ Smallest patch size may be too high for small children. For children &gt;2 yr. Apply to upper back in young children. Patch may not be cut. Typically for patients on at least 60 mg morphine/day or its equivalent. Not appropriate when dosage changes are frequent or for opioid-naïve patients. Fever &gt;40°C results in higher serum concentrations†</td>
</tr>
<tr>
<td>Pain—neuropathic</td>
<td>Nortriptyline</td>
<td>0.5 mg/kg po at bedtime to maximum of 150 mg/day</td>
<td>Fewer anticholinergic side effects than amitriptyline. May cause constipation, sedation, postural hypotension, dry mouth. May cause QT interval prolongation (consider ECG). At higher doses monitor ECG and plasma levels May cause neuropsychiatric events in children (agression, emotional lability, hyperkinesia), usually mild but may require discontinuation of gabapentin. May cause dizziness, drowsiness, tremor, nystagmus, ataxia, swelling</td>
</tr>
<tr>
<td></td>
<td>Gabapentin</td>
<td>Start at 5 mg/kg/day at bedtime and gradually increase to 10-15 mg/kg/day divided tid; titrate up by 5 mg/kg/day every 3-4 days as needed but not to exceed 50-75 mg/kg/day (3600 mg/day)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pregabalin</td>
<td>Start at 1 mg/kg/dose po at bedtime for 3 days, then increase to 1 mg/kg/dose bid. Increase every 3 days to 3 mg/kg/dose po bid (maximum: 6 mg/kg/dose)</td>
<td>See previous listing</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Morphine, immediate release (i.e., MSIR) Lorazepam</td>
<td>0.1 mg/kg po q 4 hr pm†† 0.025-0.05 mg/kg IV/po q 6 hr, up to 2 mg/dose</td>
<td>All opioids may relieve dyspnea. For dyspnea, the starting dose is 30% of the dose that would be administered for pain§</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>See previous listing</td>
</tr>
</tbody>
</table>
### Table 43-6
Pharmacologic Approach to Symptoms Commonly Experienced by Children with Life-Threatening Illness—cont’d

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>MEDICATION</th>
<th>STARTING DOSE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>Scopolamine</td>
<td>1.5 mg patch, change q 72 hr</td>
<td>Excessive drying of secretions can cause mucus plugging of airways. Good for motion-induced nausea and vomiting. Handling patch and contacting eye may cause anisocoria and blurry vision. May fold patches but do not cut them. Anticholinergic side effects possible</td>
</tr>
<tr>
<td>secretions</td>
<td>patch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycopyrrolate</td>
<td>0.04-0.1 mg/kg</td>
<td>4-8 hr</td>
<td>Powerful antiasialogogue. Excessive drying of secretions can cause mucus plugging of airways. Anticholinergic side effects possible. Quaternary ammonium structure limits its ability to cross lipid membranes, such as the blood–brain barrier (in contrast to atropine, scopolamine and hyoscyamine sulfate), so may exert fewer central anticholinergic effects</td>
</tr>
<tr>
<td>Hyoscyamine</td>
<td>4 gtt po q 4</td>
<td>4 hr pm if &lt;2 yr; 8 gtt po q 4 hr pm if 2-12 yr; do not exceed 24 gtt/24 hr</td>
<td>Anticholinergic side effects possible, including sedation. May be given sublingually</td>
</tr>
<tr>
<td>sulfate Atropine</td>
<td>1-2 gtt SL</td>
<td>4-6 hr pm</td>
<td>Give 0.5% ophthalmic drops sublingually</td>
</tr>
<tr>
<td>Nausea</td>
<td>Metoclopramide</td>
<td>0.1-0.2 mg/kg/dose q 6 hr, up to 10 mg/dose (prokinetic and mild nausea dosing). For chemotherapy-associated nausea 0.5-1 mg/kg q 6 hr pm po/IV/SC, give with diphenhydramine and continue diphenhydramine for 24 hr after last dose of high-dose metoclopramide to prevent extrapyramidal reaction</td>
<td>Helpful when dysmotility is an issue; may cause extrapyramidal reactions, particularly in children following IV administration of high doses. Contraindicated in complete bowel obstruction or pheochromocytoma</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>0.15 mg/kg dose</td>
<td>I/V/po q 8 hr pm</td>
<td>Significant experience in pediatrics. Good empiric therapy for nausea in palliative care population. Oral dissolving tablet contains phenylalanine. Higher doses used with chemotherapy although single 32 mg IV dose is no longer available (risk for QT prolongation). Consider ECG monitoring in patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias, or in patients on other medications with the potential to cause QT prolongation</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.1 mg/kg/dose</td>
<td>tid po/IV; max dose 10 mg/day</td>
<td>Also helpful with hepatic capsular distention, bowel wall edema, anorexia, increased intracranial pressure. May cause mood swings or psychosis</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>See previous</td>
<td>listing</td>
<td>See previous listing</td>
</tr>
<tr>
<td>Dronabinol</td>
<td>2.5-5 mg/m²/dose</td>
<td>q 3-4 hr</td>
<td>Available in 2.5- and 5-mg capsules. May remove liquid contents from capsules for children who cannot swallow capsules. Avoid in patients with sesame oil hypersensitivity or history of schizophrenia. May cause euphoria, dysphoria or other mood changes. Tolerance to central nervous system side effects usually develops in 1-3 days of continuous use. Avoid in patients with depression or mania</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>See previous</td>
<td>listing</td>
<td>See previous listing</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Lorazepam</td>
<td>See previous listing</td>
<td></td>
</tr>
<tr>
<td>Agitation</td>
<td>Haloperidol</td>
<td>0.01 mg/kg po tid pm for acute onset: 0.025-0.050 mg/kg po, may repeat 0.025 mg/kg in 1 hr pm</td>
<td>May cause extrapyramidal reactions, which can be reversed with diphenhydramine or Cogentin. Safety not established in children &lt;3 yr</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>Lorazepam</td>
<td>See previous listing</td>
<td></td>
</tr>
<tr>
<td>/insomnia</td>
<td>Trazodone</td>
<td>Children 6-18 yr: 0.75-1 mg/kg/dose, given bid-tid if needed If &gt;18 yr, start at 25-50 mg/dose, given bid-tid if needed</td>
<td>See previous listing Potentially arrhythmogenic</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Methylphenidate</td>
<td>0.3 mg/kg/dose titrated as needed; up to 60 mg/day</td>
<td>Rapid antidepressant effect; also improves cognition. Administer before meals to avoid appetite suppression. Use with caution in children at risk for cardiac arrhythmia. Available as liquid and chewable tablet</td>
</tr>
</tbody>
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Continued
<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>MEDICATION</th>
<th>STARTING DOSE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>Diphenhydramine</td>
<td>0.5-1 mg/kg q 6 hr IV/po (100 mg max per day)</td>
<td>May reverse phenothiazine-induced dystonic reactions. Topical formulation on large areas of the skin or open area may cause toxic reactions. May cause paradoxical reaction in young children</td>
</tr>
<tr>
<td></td>
<td>Hydroxyzine</td>
<td>0.5-1 mg/kg q 6 hr IV/po (600 mg maximum per day)</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>Docusate</td>
<td>40-150 mg/day po in 1-4 divided doses</td>
<td>Stool softener available as liquid or capsule Tasteless powder may be mixed in beverage of choice. Now available nonprescription</td>
</tr>
<tr>
<td></td>
<td>MiraLAX</td>
<td>&lt;5 yr: 1/2 scoop (8.5 g) in 4 oz of water daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;5 yr: 1 scoop (17 g) in 8 oz of water daily</td>
<td>Bowel stimulant; dosing q 2 hr may cause cramping</td>
</tr>
<tr>
<td></td>
<td>Lactulose</td>
<td>5-10 mL po up to q 2 hr until bowel movement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Senna</td>
<td>2.5 mL po daily (for children weighing &gt;27 kg)</td>
<td>Bowel stimulant; available as granules</td>
</tr>
<tr>
<td></td>
<td>Dulcolax</td>
<td>3-12 yr: 5-10 mg po daily</td>
<td>Available in oral or rectal formulation</td>
</tr>
<tr>
<td></td>
<td>Pediatric Fleets Enema</td>
<td>&gt;12 yr: 5-15 mg po daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MethylNaltrexone</td>
<td>10-20 kg: 2 mg SC</td>
<td>A peripherally acting opioid antagonist for opioid-induced constipation. Usually works within 30-60 minutes of administration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21-33 kg: 4 mg SC</td>
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<td></td>
<td></td>
<td>34-46 kg: 6 mg SC</td>
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<td></td>
<td></td>
<td>47-62 kg: 8 mg SC</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>63-114 kg: 12 mg SC</td>
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<tr>
<td></td>
<td></td>
<td>≥155 kg: 0.15 mg/kg SC</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>Lactulose</td>
<td>5-10 mL po up to q 2 hr until bowel movement</td>
<td></td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
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<td>3-12 yr: 5-10 mg po daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pediatric Fleets Enema</td>
<td>&gt;12 yr: 5-15 mg po daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MethylNaltrexone</td>
<td>10-20 kg: 2 mg SC</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>21-33 kg: 4 mg SC</td>
<td></td>
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<td></td>
<td></td>
<td>34-46 kg: 6 mg SC</td>
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<td></td>
<td></td>
<td>47-62 kg: 8 mg SC</td>
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<td></td>
<td>63-114 kg: 12 mg SC</td>
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<tr>
<td></td>
<td></td>
<td>≥155 kg: 0.15 mg/kg SC</td>
<td></td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>Diazepam</td>
<td>0.5 mg/kg/dose IV/po q 6 hr pm; initial dose</td>
<td>May be irritating if given by peripheral IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>for children &lt;5 yr is 5 mg dose; for children</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥5 yr dose is 10 mg/dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 mg po tid, increase by 5 mg/dose as needed</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>Lorazepam</td>
<td>0.1 mg/kg IV/po/SL/PR; repeat q 10 min ×2</td>
<td>May be given pr as Diastat (0.2 mg/kg/dose q 15 minutes ×3 doses)</td>
</tr>
<tr>
<td></td>
<td>Diazepam</td>
<td>0.1 mg/kg q 6 hr (max 5 mg dose if &lt;5 yr; max</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mg/dose if ≥5 yr)</td>
<td></td>
</tr>
<tr>
<td>Neuroirritability</td>
<td>Gabapentin</td>
<td>See previous listing</td>
<td>Transdermal patch may contain metal (e.g., aluminum) that may cause burns if worn during MRI scan. Remove patch prior to MRI. Patch may be cut into quarter or half fractions based on dose needed</td>
</tr>
<tr>
<td></td>
<td>Clonidine</td>
<td>Starting dose: 0.05 mg/day. May increase</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>every 3-5 days by 0.05 mg/day to 3-5 µg/kg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>given in divided doses 3-4 times/day; maximum</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>dose is 0.3 mg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>May switch from oral to transdermal route</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>once optimal oral dose is established; Transdermal</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>dose is equivalent to the total oral dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(e.g., if total oral dose is 0.1 mg/day, apply</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 patch (delivers 0.1 mg/day). Change patch</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>every 7 days. &lt;10 yr or &lt;30 kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Initial dose: 0.01-0.03 mg/kg/day divided tid;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥10 yr (≥30 kg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Initial dose: up to 0.25 mg po tid; may</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>increase by 0.5-1 mg/day every 3 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maintenance dose: 0.05-0.2 mg/kg/day up to 20</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>mg/day</td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>Megestrol acetate</td>
<td>10 mg/kg/day in 1-4 divided doses, may titrate</td>
<td>For children &gt;10 yr. Acute adrenal insufficiency may occur with abrupt withdrawal after long-term use. Use with caution in patients with diabetes mellitus or history of thromboembolism. May cause photosensitivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>up to 15 mg/kg/day or 800 mg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dronabinol</td>
<td>See previous listing</td>
<td>See previous listing Potential antihistamine and serotonin antagonist</td>
</tr>
<tr>
<td></td>
<td>Cyproheptadine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Infants <6 mo should receive 25-30% of the usual opioid starting dose.

†Although the usual opioid starting dose is presented, dose may be titrated as needed. There is no ceiling/maximum dose for opioids.

‡Breakthrough dose is 10% of 24 hr dose. See Chapter 62 for information regarding titration of opioids.

§Side effects from opioids include constipation, respiratory depression, pruritus, nausea, urinary retention, physical dependence.

ECG, electrocardiogram; gtt, drops; hr, hr; IV, intravenously; po, by mouth; pr, rectally; prn, as needed; SC, subcutaneously; SL, sublingually.

Many children with life-threatening illness experience pain that requires opioids for adequate relief at some point in their illness trajectory. Although it was previously recommended, prescribing codeine should generally be avoided because of its side-effect profile and lack of superiority over nonopioid analgesics. Furthermore, relatively common genetic polymorphisms in the CYP2D6 gene lead to wide variation in codeine metabolism. Specifically, 10-40% of individuals carry polymorphisms causing them to be “poor metabolizers” who cannot convert codeine to its active form, morphine, and therefore are at risk for inadequate pain control; others are “ultrametabolizers” who may even experience respiratory depression from rapid generation of morphine from codeine. It is therefore preferable to use a known amount of the active agent, morphine.

It is important to explore with families, as well as members of the care team, misconceptions that they may have regarding respiratory suppression, addiction, dependence, the symbolic meaning of starting an opioid such as methadone or morphine and/or a morphine drip, and the potential for opioids to hasten death. There is no association between administration or escalation of opioids and length of survival. Evidence supports longer survival in individuals with symptoms that are well controlled.

Children also often experience a multitude of nonpain symptoms. A combination of both pharmacologic (see Table 43-6) and nonpharmacologic approaches (see Table 43-7) is often optimal. Fatigue is one of the most common symptoms in children with advanced illness. Children may experience fatigue as a physical symptom (e.g., weakness or somnolence), a decline in cognition (e.g., diminished attention or concentration), and/or impaired emotional function (e.g., depressed mood or decreased motivation). Because of its multidimensional and incapacitating nature, fatigue can prevent children from participating in meaningful or pleasurable activities, thereby impairing quality of life. Fatigue is usually multifactorial in etiology. A careful history may reveal contributing physical factors (uncontrolled symptoms, medication side effects), psychological factors (anxiety, depression), spiritual distress, or sleep disturbance. Interventions to reduce fatigue include treatment of contributing factors, exercise, pharmacologic agents, and behavior modification strategies. Challenges to effectively addressing fatigue include the common belief that fatigue is inevitable, lack of communication between families and care teams about it, and limited awareness of potential interventions for fatigue.

Dyspnea (the subjective sensation of shortness of breath) is caused by a mismatch between afferent sensory input to the brain and the

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Table 43-7  Nonpharmacologic Approach to Symptoms Commonly Experienced by Children with Life-Threatening Illness

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>APPROACH TO MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Prevent pain when possible by limiting unnecessary painful procedures, providing sedation, and giving pre-emptive analgesia prior to a procedure (e.g., including sucrose for procedures in neonates) Address coincident depression, anxiety, sense of fear or lack of control Consider guided imagery, relaxation, hypnosis, art/pet/play therapy, acupuncture/acupressure, biofeedback, massage, heat/cold, yoga, transcutaneous electric nerve stimulation, distraction</td>
</tr>
<tr>
<td>Dyspnea or air hunger</td>
<td>Suction secretions if present, positioning, comfortable loose clothing, fan to provide cool, blowing air Limit volume of IV fluids, consider diuretics if fluid overload/pulmonary edema present Behavioral strategies including breathing exercises, guided imagery, relaxation, music, distraction</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Sleep hygiene (establish a routine, promote habits for restorative sleep) Regular, gentle exercise; Prioritize or modify activities Address potentially contributing factors (e.g., anemia, depression, side effects of medications) Aromatherapy*: peppermint, rosemary, basil</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>Consider dietary modifications (bland, soft, adjust timing/volume of foods or feeds) Aromatherapy*: ginger, peppermint, lavender acupuncture/acupressure</td>
</tr>
<tr>
<td>Constipation</td>
<td>Increase fiber in diet, encourage fluids, ambulation (if possible)</td>
</tr>
<tr>
<td>Oral lesions/dysphagia</td>
<td>Oral hygiene and appropriate liquid, solid and oral medication formulation (texture, taste, fluidity). Treat infections, complications (mucositis, pharyngitis, dental abscess, esophagitis) Oropharyngeal motility study and speech (feeding team) consultation</td>
</tr>
<tr>
<td>Anorexia/cachexia</td>
<td>Manage treatable lesions causing oral pain, dysphagia, or anorexia. Support caloric intake during phase of illness when anorexia is reversible. Acknowledge that anorexia/cachexia is intrinsic to the dying process and may not be reversible Prevent/treat coexisting constipation</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Moisturize skin Trim child’s nails to prevent excoriation Try specialized antitch lotions Apply cold packs Counterstimulation, distraction, relaxation</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Evaluate/treat if due to obstruction Assess and treat infection Dietary modification</td>
</tr>
<tr>
<td>Depression</td>
<td>Psychotherapy, behavioral techniques, setting attainable daily goals Aromatherapy*: bergamot, lavender</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Psychotherapy (individual and family), behavioral techniques Aromatherapy*: clary sage, angelica, mandarin, lavender</td>
</tr>
<tr>
<td>Agitation/terminal restlessness</td>
<td>Evaluate for organic or drug causes Educate family Orient and reassure child; provide calm, nonstimulating environment, use familiar music, verse, voice, touch Aromatherapy*: frankincense, ylang ylang</td>
</tr>
</tbody>
</table>

*Best if aromatherapy is administered by a practitioner trained in aromatherapy.

As death approaches, a buildup of secretions may result in noisy respiration sometimes referred to as a “death rattle.” Patients at this stage are usually unconscious, and noisy respirations are often more distressing for others than for the child. It is often helpful to discuss this anticipated phenomenon with families in advance, and if it occurs, to point out the child’s lack of distress from it. If treatment is needed, an anticholinergic medication, such as glycopyrrolate, may reduce secretions.

Neurologic symptoms include seizures that are often part of the antecedent illness but may increase in frequency and severity toward the end of life. A plan for managing seizures should be made in advance and anticonvulsants should be readily available in the event of seizure. Parents can be taught to use rectal diazepam at home. Increased neuroirritability accompanies some neurodegenerative disorders; it may be particularly disruptive because of the resultant break in normal sleep–wake patterns and the difficulty in finding respite facilities for children who have prolonged crying. Such neuroirritability may respond to gabapentin. Judicious use of sedatives, benzodiazepines, clonidine, or nortriptyline, or methadone may also reduce irritability without inducing excessive sedation; such treatment can dramatically improve the quality of life for both child and caregivers. Increased intracranial pressure and spinal cord compression are most often encountered in children with brain tumors or metastatic and solid tumors. Depending on the clinical situation and the goals of care, radiation therapy, surgical interventions, and steroids are potential therapeutic options.

Feeding and hydration issues can raise ethical questions that evoke intense emotions in families and medical caregivers alike. Options that may be considered to artificially support nutrition and hydration in a child who can no longer feed by mouth include nasogastric and gastrostomy feedings or intravenous nutrition or hydration. These complex decisions require evaluating the risks and benefits of artificial feedings and taking into consideration the child’s functional level and prognosis. At times, it may be appropriate to initiate a trial of tube feedings with the understanding that they may be discontinued at a later stage of the illness. A commonly held but unsubstantiated belief is that artificial nutrition and hydration are “comfort measures,” without which a child may suffer from starvation or thirst. This may result in well-meaning but disruptive and invasive attempts to administer nutrition or fluids to a dying child. In dying adults, the sensation of thirst may be alleviated by careful efforts to keep the mouth moist and clean. There may also be deleterious side effects to artificial hydration in the form of increased secretions, need for frequent urination, edema and exacerbation of dyspnea. For these reasons, it is important to educate families about anticipated decreases in appetite/thirst and therefore little need for nutrition and hydration as the child approaches death. In addition, exploring the meaning that provision of nutrition and hydration may hold for families, as well as helping families anticipate the changes in their child’s appearance and exploration of sorrow and loneliness that they may love and nurture their child, may ease distress around this issue. Nausea and vomiting may be the result of a variety of causes, including medications/toxins, irritation to or obstruction of the gastrointestinal tract, motion, and emotions. Drugs such as metoclopramide, 5-hydroxytryptamine antagonists, steroids, and aprepitant may be used, and should be chosen depending on the underlying pathophysiology and neurotransmitters involved. Vomiting may accompany nausea but may also occur without nausea, such as in the instance of increased intracranial pressure. Constipation is commonly encountered in children with neurologic impairment or children receiving medications that impair gastrointestinal motility (most notably, opioids). Stool frequency and quantity should be evaluated in the context of the child’s diet and usual bowel pattern. Children on regular opioids should routinely be placed on stool softeners (docusate) in addition to a laxative agent (e.g., senna). Diarrhea may be particularly difficult for the child and family and may be treated with loperamide (an opioid that does not cross the blood–brain barrier), and in some cases cholestyramine or octreotide may be indicated. Paradoxical diarrhea, a result of overflow resulting from constipation, should also be included in the differential diagnosis.

Hematologic issues include consideration of anemia and thrombocytopenia or bleeding. If the child has symptomatic anemia (weakness, listlessness, shortness of breath, tachycardia), red blood cell transfusions may be considered. Platelet transfusions may be an option if the child has symptoms of bleeding. Life-ending hemorrhage is disturbing for all concerned, and a plan involving the use of fast-acting sedatives should be prepared in advance if such an event is a possibility.

Skin care issues include primary prevention of problems by ongoing and timely assessment including observation of indwelling lines and tubes, and frequent turning and repositioning and alleviating pressure wherever possible (e.g., elevating heels with pillows). Pruritus may be secondary to systemic disorders or drug therapy. Treatment includes avoiding excessive use of drying soaps, using moisturizers, trimming fingernails, and wearing loose-fitting clothing, in addition to administering topical or systemic steroids. Oral antihistamines and other specific therapies may also be indicated (e.g., cholestyramine in biliary disease). Although opioids can cause histamine release from mast cells, this does not account for most of the pruritus caused by opioids. A trial of diphenhydramine may provide relief; alternatively, rotating opioids or instituting a low dose of opioid antagonist may be needed for refractory pruritus.

Children with life-threatening illness may experience psychological symptoms such as anxiety and depression. Such symptoms are frequently multifactorial, and sometimes interrelated with uncontrolled symptoms such as pain and fatigue. Diagnosing depression in the context of serious illness may pose challenges since neurovegetative symptoms may not be reliable indicators. Instead, expressions of hopelessness, helplessness, worthlessness, and guilt may be more useful. Pharmacologic agents such as antidepressants may be helpful, although their effect is often preceded by a significant lag phase. Because of its immediate and positive effect on mood, methylphenidate may be an effective antidepressant for children at end of life, when there may not be time for a traditional antidepressant to take effect. Interventions and opportunities for children to explore worries, hopes, and concerns in an open, supportive, and nonjudgmental setting are equally if not more important approaches to psychological distress. Skilled members from a variety of disciplines, including psychology, social work, chaplaincy, child life, and expressive therapy, among others, may help children and their families in this regard. Such opportunities may in fact create positive moments in which meaning, connection, and new definitions of hope are found.

Discussions with adolescent patients or with the parents of any ill child, about possible therapies or interventions should include integrative therapies such as massage therapy, Reiki, acupuncture, clinical aromatherapy, prayer, and nutritional supplements. Many families use integrative therapy, but do not bring it up with their physician unless explicitly asked (see Chapter 64). Although largely unproven, some therapies are inexpensive and provide relief to individual
patients. Other therapies may be expensive, painful, intrusive, and even toxic. By initiating conversation and inviting discussion in a nonjudgmental way, the clinician can offer advice on the safety of different therapies and may help avoid expensive, dangerous, or burdensome interventions.

**Intensive Symptom Management**

At end of life, when intensive efforts to relieve the symptom have been exhausted, or when efforts to address suffering are incapable of providing relief with acceptable toxicity/morbidity or in an acceptable time frame, **palliative sedation** may be considered. Palliative sedation may relieve suffering from refractory symptoms by reducing a child’s level of consciousness. It is most often used for intractable pain, dyspnea, or agitation, but is not limited to these distressing indications. Palliative sedation requires opportunities for parents, staff, and primary clinicians to discuss the indication and goals for sedation, as well as questions or concerns about this therapy, both before and after initiation of sedation.

The principle of double effect is often invoked to justify escalation of symptom-relieving medications or palliative sedation for uncontrolled symptoms at the end of life. Use of this principle emphasizes the risk of hastening death posed by escalating opioids or sedation, which is theoretical and unproven. There is mounting evidence that patients with well-controlled symptoms live longer.

**The Terminal Phase**

As death seems imminent, the major task of the physician and team are to help the child have as many good days as possible and not suffer. If not already in place, a referral to hospice may provide the most comprehensive care for the child and family. Gently preparing the family for what to expect and offering choices, when possible, will allow them a sense of control in the midst of tragic circumstances. Before death, it can be very helpful to discuss:

- Support of siblings or other family members
- Resuscitation status
- Limiting technology when no longer beneficial to the child
- Cultural, spiritual, or religious needs
- Location of death
  - Who will pronounce if death occurs at home
- Funeral arrangements
  - Offering siblings choice and appropriate support to attend
  - Autopsy and/or tissue or organ donation
  - Legacy building, benefits others, informs science and family

Offered the opportunity, families will often tolerate thinking and speaking about their hopes and fears regarding their child’s end of life, and some even express relief when the door to such conversation is opened by the care team. It may help to let the family know these conversations are not about whether the child will die, but about how the child may die.

Families gain tremendous support from having a physician and team who will continue to stay involved in the child’s care. If the child is at home or hospitalized, regular phone calls or visits, assisting with symptom management, and offering emotional support is invaluable for families.

In an intensive care setting, where technology can be overwhelming and put distance between the child and parent, the physician can offer discontinuation of that which is not benefiting the child or adding to quality of life. Parents may be afraid to ask about holding or sleeping next to their child. They may need reassurance and assistance in holding, touching, and speaking with their child, despite tubes and technology, even if the child appears unresponsive.

It is believed that hearing and the ability to sense touch is often present until death; all family members should be encouraged to continue interacting with their loved one through the dying process. Parents may be afraid to leave the bedside so that their child will not die alone. Offering parents other supports such as chaplaincy/clergy, social work and extended family members may be helpful. In most instances the moment of death cannot be predicted. Some propose that children wait to die until parents are “ready,” an important event has passed, or until they are given permission. Caregivers need not dispute this, nor the hope for a miracle often held by families until the child takes the very last breath.

For the family, the moment of death is an event that is recalled in detail for years to come, and so enhancing opportunity for dignity and limited suffering is essential. Research suggests that improved symptom control and easing of difficult moments at the time of death may lessen the long-term distress of bereaved parents. Clinical experience has shown that families often find solace in clinician “presence,” whether at home or in the hospital. After death, families should be given the option of remaining with their child for as long as they would like. During this time, physicians and other professionals may ask permission to “say goodbye.” The family may be invited to bathe and dress the body as a final act of caring for the child.

The physician’s decision to attend the funeral is a personal one. Participation may serve the dual purpose of showing respect as well as helping the clinician cope with a personal sense of loss. If unable to attend services, families report highly valuing the importance of receiving a card or note from the physician. To know that their child made a difference and will not be forgotten is often very important to families in their bereavement.

**The Pediatrician**

While optimal palliative care for children entails caregivers from a variety of disciplines, pediatricians are well-positioned to support children and their families, particularly if they have a long-standing relationship with multiple family members. A pediatrician who has cared for a family over time may already know and care for other family members, understand preexisting stressors for the family, and may be familiar with coping strategies used by family members. Pediatricians are familiar with the process of eliciting concerns and providing anticipatory guidance for parents, as well as developmentally appropriate explanations for children.

*Bibliography is available at Expert Consult.*
Bibliography
Nutritional intakes for infants, children, and adolescents should provide for maintenance of current weight and support normal growth and development. The infancy growth period is rapid, critical for neurocognitive development, and has the highest energy and nutrient requirements relative to body size compared with other periods of growth. It is followed by the childhood period of growth, during which 60% of total growth occurs, and is finally followed by the puberty phase. Nutrition and growth during the first 3 years of life predict adult stature and some health outcomes. The major risk period for growth stunting (impaired linear growth) is between 4 and 24 months of age. It is critical to identify nutrient deficiencies promptly and to address them aggressively early in life, because they can impart lasting adverse effects on growth and development. Dietary intake not only meets energy requirements but also provides macronutrients and micronutrients essential for sustaining the functioning of multiple vital processes. Nutrient deficiencies can limit growth, impair immune function, and increase morbidity and mortality. The significant global burden of malnutrition and undernutrition is the leading worldwide cause of acquired immunodeficiency and the major underlying factor for morbidity and mortality globally for children <5 yr of age.

The nutrition transition in many developing countries as populations change from traditional diets to the Western diet has resulted in increased life expectancy and adult stature in these populations. Unfortunately, this nutrition transition is also frequently accompanied by decreased physical activity, and in parallel to decreases in the incidence and prevalence of communicable (infectious) diseases, there are increases in the incidence and prevalence of noncommunicable diseases such as noninsulin-dependent diabetes, cardiovascular disease, obesity, inflammatory bowel disease, and certain cancers.

Consequently, it is important to view the impact of nutrition on health from various perspectives: to prevent deficiency, to promote adequacy, and to prevent or reduce the risk for acquiring diseases associated with excess intakes, such as obesity, diabetes, and cardiovascular disease. Advances in our understanding of the roles of vitamin D, polyunsaturated fatty acids (PUFAs), and total fiber have changed our focus from recommendations for deficiency to nutritional intakes associated with optimal health. In addition, the 2006 World Health Organization (WHO) growth charts, which are recommended for all children until 2 years of age, are not only descriptive, but are also prescriptive on how children with adequate nutrition and health care should grow. Identification and provision of appropriate and adequate nutrition in infancy and childhood are critical to not only support normal growth and development, but also to provide the foundation for lifelong health and well-being.

**DIETARY REFERENCE INTAKES**

The dietary reference intake (DRI) established by the Food and Nutrition Board of the Institute of Medicine provides guidance as to nutrient needs for individuals and groups across different life stages and by gender (Tables 44-1 to 44-4).

Key DRI concepts include the estimated average requirement (EAR), the recommended dietary allowance (RDA), and the tolerable upper limit of intake (UL) (Fig. 44-1). The EAR is the average daily nutrient intake level estimated to meet the requirements for 50% of the population, assuming normal distribution; the RDA is an estimate of the daily average nutrient intake to meet the nutritional needs of >97% of the individuals in a population, and it can be used as a guideline for individuals to avoid deficiency in the population. When an EAR cannot be derived, an RDA cannot be calculated; therefore, an adequate intake (AI) is developed as a guideline for individuals based on the best available data and scientific consensus. The UL denotes the highest average daily intake at which no adverse health effects are associated for almost all individuals in a particular group. The relationships among EAR, RDA, and UL are characterized in Figure 44-2.

**ENERGY**

Energy includes both intake and expenditure. Deficits and excesses of energy intake yield undesirable health consequences. Inadequate energy intake can lead to growth faltering, catabolism of body tissues and inability to provide energy substrate, whereas excess energy intakes can increase the risk for obesity. Adequacy of energy intake in adults is associated with maintenance of a healthy weight. The 3 components of energy expenditure in adults are the basal metabolic rate, thermal effect of food (energy required for digestion and absorption), and energy for physical activity. Additional energy intake is required to support growth and development for children.

The estimated energy requirement (EER) is the average dietary energy intake predicted to maintain energy balance in a healthy individual and accounts for age, gender, weight, stature, and physical activity level (see Table 44-1). The Dietary Guidelines for Americans 2010 recommend 60 min of moderately intense daily activity for children >2 yr of age to maintain a healthy weight and to prevent or delay progression of chronic noncommunicable diseases such as obesity and cardiovascular disease. The EER was determined based on empirical research in healthy persons at different physical activity levels, including levels different from the recommended levels. They do not necessarily apply to children with acute or chronic diseases. EER is estimated by equations that account for total energy expenditure, as well as energy deposition for healthy growth. The EER for infants, relative to body weight, are approximately twice those for adults because of the increased metabolic rate and requirements for weight maintenance and tissue accretion affecting growth.

The nutrients that provide energy intake in the child's diet are fats (~9 kcal/g), carbohydrates (~4 kcal/g), and proteins (~4 kcal/g). They are referred to as **macronutrients**. Alcohol intake also contributes to energy intake (~7 kcal/g). The EER does not specify the relative energy contributions of macronutrients. Once the minimal intakes of each of the respective macronutrients are attained to meet physiologic requirements and to achieve adequacy (sufficient protein intake to meet specific amino acid requirements, fat for essential fatty acids, and neurologic development), the remainder of the intake is used to meet energy requirements with some degrees of freedom and interchangeability among fats, carbohydrates, and proteins. This forms the basis for the acceptable macronutrient distribution ranges (AMDRs) (see Table 44-2), expressed as a function of total energy intake.
Equations to Estimate Energy Requirement

### INFANTS AND YOUNG CHILDREN: EER (KCAL/DAY) = TEE + ED

<table>
<thead>
<tr>
<th>Age (mo)</th>
<th>EER Formula</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3 mo</td>
<td>EER = (89 x weight [kg]) – 100 + 175</td>
<td>kcal/day</td>
</tr>
<tr>
<td>4-6 mo</td>
<td>EER = (89 x weight [kg]) – 100 + 56</td>
<td>kcal/day</td>
</tr>
<tr>
<td>7-12 mo</td>
<td>EER = (89 x weight [kg]) – 100 + 22</td>
<td>kcal/day</td>
</tr>
<tr>
<td>13-36 mo</td>
<td>EER = (89 x weight [kg]) – 100 + 20</td>
<td>kcal/day</td>
</tr>
</tbody>
</table>

### CHILDREN AND ADOLESCENTS 3-18 YR: EER (KCAL/DAY) = TEE + ED

#### Boys
- 3-8 yr: EER = 88.5 – (61.9 x age [yr] + PA x [(26.7 x weight [kg]) + (903 x height [m])] + 20
- 9-18 yr: EER = 88.5 – (61.9 x age [yr] + PA x [(26.7 x weight [kg]) + (903 x height [m])] + 25

#### Girls
- 3-8 yr: EER = 135.3 – (30.8 x age [yr] + PA x [(10 x weight [kg]) + (934 x height [m])] + 20
- 9-18 yr: EER = 135.3 – (30.8 x age [yr] + PA x [(10 x weight [kg]) + (934 x height [m])] + 25

ED, energy deposition; EER, estimated energy requirement; TEE, total energy expenditure.

PA indicates the physical activity coefficient:
- For boys:
  - PA = 1.00 (sedentary, estimated physical activity level 1.0-1.4)
  - PA = 1.13 (low active, estimated physical activity level 1.4-1.6)
  - PA = 1.26 (active, estimated physical activity level 1.6-1.9)
  - PA = 1.42 (very active, estimated physical activity level 1.9-2.5)

- For girls:
  - PA = 1.00 (sedentary, estimated physical activity level 1.0-1.4)
  - PA = 1.16 (low active, estimated physical activity level 1.4-1.6)
  - PA = 1.31 (active, estimated physical activity level 1.6-1.9)
  - PA = 1.56 (very active, estimated physical activity level 1.9-2.5)

Adapted from Kleinman RE, editor: Pediatric nutrition handbook, ed 6, Elk Grove Village, IL, 2009, American Academy of Pediatrics.

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### FEAT

Fat is the most calorically dense macronutrient, providing approximately 9 kcal/g. For infants, human milk/formula are the main dietary sources of fat, whereas older children get fat from animal products, vegetable oils, and margarine. The AMDR for fats is 30-40% of total energy intake for children 1-3 yr and 25-35% for children 4-18 yr of age. In addition to being energy-dense, fats provide essential fatty acids and play structural and functional roles; cholesterol moieties are precursors for cell membranes, hormones, and bile acids. Fat intake facilitates absorption of fat-soluble vitamins A, D, E, and K. Both roles are particularly relevant in the context of neurological and ocular development.

#### Table 44-2  Acceptable Macronutrient Distribution Ranges

<table>
<thead>
<tr>
<th>Macronutrient</th>
<th>AMDR (% of Energy</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat</td>
<td>30-40</td>
<td>25-35</td>
</tr>
<tr>
<td>ω6 PUFAs</td>
<td>5-10</td>
<td>5-10</td>
</tr>
<tr>
<td>ω3 PUFAs</td>
<td>0.6-1.2</td>
<td>0.6-1.2</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>45-65</td>
<td>45-65</td>
</tr>
<tr>
<td>Protein</td>
<td>5-20</td>
<td>10-30</td>
</tr>
</tbody>
</table>

AMDR, acceptable macronutrient distribution range; PUFA, polyunsaturated fatty acid.


---

### Table 44-3  Dietary Reference Intakes: Macronutrients

<table>
<thead>
<tr>
<th>Function</th>
<th>Life Stage Group</th>
<th>RDA or AI* (g/day)</th>
<th>Selected Food Sources</th>
<th>Adverse Effects of Excessive Consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL DIGESTIBLE CARBOHYDRATE</td>
<td><strong>Infants</strong></td>
<td></td>
<td>Major types: starches and sugars</td>
<td>No defined intake level for potential adverse effects of total digestible carbohydrate is identified, but the upper end of the AMDR was based on decreasing risk of chronic disease and providing adequate intake of other nutrients. It is suggested that the maximal intake of added sugars be limited to providing no more than 25% of energy.</td>
</tr>
<tr>
<td></td>
<td>0-6 mo</td>
<td>60*</td>
<td>Grains and vegetables (corn, pasta, rice, potatoes, breads) are sources of starch</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7-12 mo</td>
<td>95*</td>
<td>Natural sugars are found in fruits and juices</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;1 yr</td>
<td>130</td>
<td>Sources of added sugars: soft drinks, candy, fruit drinks, desserts</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pregnancy</td>
<td>≤18 yr 175</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>19-30 yr 175</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL FIBER</td>
<td><strong>Infants</strong></td>
<td></td>
<td>Includes dietary fiber naturally present in grains (e.g., oats, wheat, unrefined rice) and functional fiber synthesized or isolated from plants or animals and shown to be of benefit to health</td>
<td>Dietary fiber can have variable compositions; therefore, it is difficult to link a specific source of fiber with a particular adverse effect, especially when phytate is also present in the natural fiber source. As part of an overall healthy diet, a high intake of dietary fiber will not produce deleterious effects in healthy persons. Occasional adverse GI symptoms are observed when consuming some isolated or synthetic fibers, but serious chronic adverse effects have not been observed. Owing to the bulky nature of fibers, excess consumption is likely to be self-limiting; therefore, an UL was not set for individual functional fibers.</td>
</tr>
<tr>
<td>Improves laxation, reduces risk of coronary heart disease, assists in maintaining normal blood glucose levels</td>
<td>0-6 mo</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7-12 mo</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Children</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1-3 yr</td>
<td>190*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4-8 yr</td>
<td>25*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9-13 yr</td>
<td>31*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14-18 yr</td>
<td>38*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19-21</td>
<td>38*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9-13 yr</td>
<td>26*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14-18 yr</td>
<td>26*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19-21 yr</td>
<td>25*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pregnancy</td>
<td>≤18 yr 28*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>19-21 yr 28*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>FUNCTION</th>
<th>LIFE STAGE GROUP</th>
<th>RDA OR AI* (g/day)</th>
<th>SELECTED FOOD SOURCES</th>
<th>ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOTAL FAT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Energy source</td>
<td>Infants 0-6 mo</td>
<td>31*</td>
<td>Human milk or infant formula</td>
<td>UL not set because there is no defined intake of fat at which adverse effects occur.</td>
</tr>
<tr>
<td>When found in foods, is a source of ω3 and ω6 PUFAs</td>
<td>Infants 7-12 mo 1-18 yr</td>
<td>30*</td>
<td>Older children: butter, margarine, vegetable oils, whole milk, visible fat on meat and poultry products, invisible fat in fish, shellfish, some plant products such as seeds and nuts, bakery products</td>
<td>High fat intake will lead to obesity. The upper end of AMDR is also based on decreasing risk of chronic disease and providing adequate intake of other nutrients</td>
</tr>
<tr>
<td>Facilitates absorption of fat-soluble vitamins</td>
<td>Infants 0-6 mo</td>
<td>4.4*</td>
<td>Nuts, seeds; vegetable oils such as soybean, safflower, corn oil</td>
<td>Low fat intake (with high carbohydrate) has been shown to increase plasma triacylglycerol concentrations and decrease HDL cholesterol</td>
</tr>
<tr>
<td><strong>w6 POLYUNSATURATED FATTY ACIDS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Essential component of structural membrane lipids, involved with cell signaling, precursor of eicosanoids</td>
<td>Infants 0-6 mo</td>
<td>4.4*</td>
<td>Vegetable oils, e.g., soybean, canola, flax seed oil; fish oils, fatty fish; smaller amounts in meats and eggs</td>
<td>No defined intake of w6 level at which adverse effects occur</td>
</tr>
<tr>
<td>Required for normal skin function</td>
<td>Children</td>
<td>4.6*</td>
<td></td>
<td>Upper end of the AMDR is based on the lack of evidence that demonstrates long-term safety and human in vitro studies that show increased free-radical formation and lipid peroxidation with higher amounts of w6 fatty acids</td>
</tr>
<tr>
<td></td>
<td>1-3 yr</td>
<td>7*</td>
<td></td>
<td>Lipid peroxidation is thought to be a component of atherosclerotic plaques</td>
</tr>
<tr>
<td></td>
<td>4-8 yr</td>
<td>10*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Males</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9-13 yr</td>
<td>12*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14-18 yr</td>
<td>16*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19-21 yr</td>
<td>17*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-6 mo</td>
<td>10*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7-12 mo</td>
<td>11*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19-21 yr</td>
<td>12*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pregnant Female</td>
<td>≤18 yr</td>
<td>13*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lactating Female</td>
<td>≤18 yr</td>
<td>13*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>19-21 yr</td>
<td>13*</td>
<td></td>
</tr>
<tr>
<td><strong>w3 POLYUNSATURATED FATTY ACIDS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Involved with neurologic development and growth</td>
<td>Infants 0-6 mo</td>
<td>0.5*</td>
<td>Vegetable oils, e.g., soybean, canola, flax seed oil; fish oils, fatty fish; smaller amounts in meats and eggs</td>
<td>No defined intake level for potential adverse effects of w3 PUFAs is identified</td>
</tr>
<tr>
<td>Precursor of eicosanoids</td>
<td>Infants 7-12 mo</td>
<td>0.5*</td>
<td></td>
<td>Upper end of AMDR is based on maintaining the appropriate balance with w6 fatty acids and on the lack of evidence that demonstrates long-term safety, along with human in vitro studies that show increased free-radical formation and lipid peroxidation with higher amounts of PUFAs</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>0.7*</td>
<td></td>
<td>Because the longer-chain n-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are biologically more potent than their precursor, linolenic acid, much of the work on the adverse effects of this group of fatty acids has been on DHA and EPA</td>
</tr>
<tr>
<td></td>
<td>1-3 yr</td>
<td>0.9*</td>
<td></td>
<td>Lipid peroxidation is thought to be a component of atherosclerotic plaques</td>
</tr>
<tr>
<td></td>
<td>4-8 yr</td>
<td>1.2*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Males</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9-13 yr</td>
<td>1.6*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14-18 yr</td>
<td>1.6*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19-21 yr</td>
<td>1.6*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-6 mo</td>
<td>1.0*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7-12 mo</td>
<td>1.1*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19-21 yr</td>
<td>1.1*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pregnant Female</td>
<td>≤18 yr</td>
<td>1.1*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lactating Female</td>
<td>≤18 yr</td>
<td>1.4*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>19-21 yr</td>
<td>1.4*</td>
<td></td>
</tr>
<tr>
<td><strong>SATURATED AND TRANS FATTY ACIDS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The body can synthesize its needs for saturated fatty acids from other sources</td>
<td>Infants</td>
<td></td>
<td>Saturated fatty acids are present in animal fats (meat fats and butter fat), and coconut and palm kernel oils</td>
<td>There is an incremental increase in plasma total and LDL cholesterol concentrations with increased intake of saturated or trans fatty acids; therefore, the intakes of each should be minimized while consuming a nutritionally adequate diet</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Trans fat: stick margarines, foods containing hydrogenated or partially hydrogenated vegetable shortenings</td>
<td></td>
</tr>
</tbody>
</table>
Table 44-3  Dietary Reference Intakes: Macronutrients—cont’d

<table>
<thead>
<tr>
<th>FUNCTION</th>
<th>LIFE STAGE GROUP</th>
<th>RDA OR AI* (g/day)</th>
<th>SELECTED FOOD SOURCES</th>
<th>ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOLESTEROL</td>
<td></td>
<td>No dietary requirement</td>
<td>Sources: liver, eggs, foods that contain eggs, e.g., cheesecake, custard pie</td>
<td></td>
</tr>
<tr>
<td>PROTEIN AND AMINO ACIDS†</td>
<td>Infants 0-6 mo</td>
<td>9.1*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7-12 mo</td>
<td>11.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Children 1-3 yr</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4-8 yr</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Males 9-13 yr</td>
<td>34</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14-18 yr</td>
<td>52</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥19 yr</td>
<td>56</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Females 9-13 yr</td>
<td>34</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥14 yr</td>
<td>46</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤18 yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19-21 yr</td>
<td>71</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Starred numbers are AI; bold numbers are RDA. RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of 97-98% of members in a group. For healthy breast-fed infants, the AI is the mean intake. The AI for other life-stage and gender groups is believed to cover the needs of all members of the group, but lack of data prevents specifying with confidence the percentage covered by this intake. AMDR is the range of intake for a particular nutrient, across the entire life span of healthy individuals. Higher end of AMDR was based on complementing the AMDR for carbohydrate and fat for the various age groups. Lower end of AMDR is set at approximately the RDA.

Table 44-4  Indispensable, Dispensable, and Conditionally Indispensable Amino Acids in the Human Diet

<table>
<thead>
<tr>
<th>INDISPENSABLE</th>
<th>DISPENSABLE</th>
<th>CONDITIONALLY INDISPENSABLE*</th>
<th>PRECURSORS OF CONDITIONALLY INDISPENSABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histidine†</td>
<td>Alanine</td>
<td>Arginine</td>
<td>Glutamine/glutamate, aspartate</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>Aspartic acid</td>
<td>Cysteine</td>
<td>Methionine, serine</td>
</tr>
<tr>
<td>Leucine</td>
<td>Asparagine</td>
<td>Glutamine</td>
<td>Glutamic acid/ammonia</td>
</tr>
<tr>
<td>Lysine</td>
<td>Glutamic acid</td>
<td>Glycine</td>
<td>Serine, choline</td>
</tr>
<tr>
<td>Methionine</td>
<td>Serine</td>
<td>Proline</td>
<td>Glutamate</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td></td>
<td>Tyrosine</td>
<td>Phenylalanine</td>
</tr>
<tr>
<td>Threonine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tryptophan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Conditionally indispensable is defined as requiring a dietary source when endogenous synthesis cannot meet metabolic need.
†Although histidine is considered indispensable, unlike the other 8 indispensable amino acids, it does not fulfill the criteria of reducing protein deposition and inducing negative nitrogen balance promptly upon removal from the diet.
Triglycerides are the most common form of dietary fat and are composed of 1 glycerol molecule and 3 fatty acids. Triglycerides are found in animal and vegetable fats. Simple sugars (refined grains and high sugar drinks) are converted to triglycerides in the liver. Elevated serum triglycerides are a risk factor for cardiovascular disease and part of the metabolic syndrome. Decreasing simple sugars and increasing complex carbohydrate intake reduce serum triglyceride levels.

Dietary saturated fatty acids (found primarily in animal fat and dairy products), trans fats (found in hydrogenated margarines and oils), and cholesterol increase the low-density lipoprotein (LDL) fraction of serum cholesterol, a risk factor for the development of atherosclerosis. Autopsies studies demonstrate that atherosclerosis begins early in childhood, even in infancy. Therefore, dietary advice to optimize cardiovascular health should be dispensed for children starting at age 2 yr when sufficient fat intake to sustain growth and brain development is less of a concern.

Because saturated and monounsaturated fats can be synthesized endogenously to support adequate structural and physiologic requirements, there is no AI or RDA set for these dietary components. Trans fats have no known beneficial effects in humans; therefore, no corresponding AI or RDA has been set. Similarly, an UL has not been set for cholesterol, saturated, or trans fats because there is a positive linear association between intake of these fats and increased risk for cardiovascular disease, without a threshold level at which risk is increased. Diets low in saturated fats and cholesterol and without trans fats are therefore preferred. For optimal cardiovascular health in the general population, rather than limiting the total amount of fat intake, in most cases, advice should focus on changing the type of fat that is consumed. With respect to preventing obesity, all types of fatty acids have about the same energy content and can contribute to increasing the risk for obesity. The current dietary guidelines for children and adolescents recommend that total fat should account for <30% of total daily energy and saturated fat less than 10%, dietary cholesterol <300 mg/day, with no trans fat.

Humans are incapable of synthesizing the precursor omega (ω) 3 (α-linolenic acid; ALA) and ω6 (linoleic acid; LA) PUFAs, and are dependent on diet for these essential fatty acids. Essential fatty acid (EFA) deficiency is associated with desquamating skin rashes, alopecia, thrombocytopenia, impaired immunity, and growth deficits, but is rare in the general population. Essential fatty acids are enzymatically elongated and desaturated into longer-chain fatty acids; ALA can be converted to eicosapentaenoic (EPA) and docosahexaenoic (DHA) ω3 PUFAs. LA is converted to arachidonic acid (ARA). Long-chain PUFAs such as DHA and ARA play a variety of structural and functional roles; they influence membrane fluidity and function as well as gene expression, and modulate the inflammatory response. ARA and DHA are present in breast milk, often supplemented in infant formulas, and are required for normal growth and development. DHA is present in the retina and is involved in the visual evoked response in infants.

The conversion of ALA to EPA and DHA and of LA to ARA is influenced by many factors, including type and amounts of dietary fats and by enzymatic substrate affinity among competing ω3, ω6, ω9, saturated, and trans fatty acids. The efficiency in conversion of ALA to a longer-chain PUFA is minimal and variable. Approximately 0.5% of dietary ALA is converted to DHA and 5% of ALA intake converted to EPA; therefore, dietary intake of longer-chain PUFAs is an important determinant of serum and tissue long-chain PUFA status. The biologic activity and health benefits of ALA are thought to be derived via the longer-chain PUFA products EPA and DHA. Consistent with these findings of limited conversion of ALA to EPA and DHA, and that EPA and DHA appear to confer the biologic role and health benefits, the DRI stipulates that up to 10% of the AI for ω3 PUFAs (ALA being the major dietary constituent) can be replaced by DHA and EPA to support normal neural development and growth.

The ratio of dietary intake of each type of PUFA influences their relative amounts in different tissue compartments. A dietary ω6:ω3 PUFA ratio of 4-5:1 may be beneficial in reducing risk of disease and may be associated with improved health outcomes, as compared to the current 15-30:1 ratio observed in the United States.

PROTEINS

Proteins and amino acids have structural and functional roles in every cell in the body. Proteins also provide approximately 4 kcal/g; however, dietary protein intake is required to replenish the turnover of proteins and to meet amino acid needs for growth. Dietary protein intake also provides energy substrate when in excess or during periods of catabolism. Inadequate energy intake and/or inadequate protein intake increases catabolism of body protein reservoirs (i.e., lean body mass) so as to provide substrate for energy and free amino acids required to support normal physiologic function. Nitrogen losses, derived from proteins, occur through urine, stool, and other bodily excretions. Increased protein intake may be required for rare hypermetabolic states, such as extensive burns. Protein energy malnutrition, although relatively rare in the noninstitutionalized U.S. population, is more common in the developing world. Protein energy malnutrition impairs brain, immune system and intestinal mucosal functions.

DRI for protein is provided in Table 44-3. An UL for protein has not been set. Intake of proteins or specific amino acids needs to be limited in some health conditions, such as renal disease and metabolic diseases, such as phenylketonuria and maple syrup urine disease, in which specific amino acids can be toxic.

The amino acid content of dietary protein is also important. Certain amino acids are indispensable and humans depend on dietary sources to meet adequacy and prevent deficiency. Certain amino acids are
termed **conditional essential/indispensable**, meaning they become essential in patients affected by some diseases or during a certain life stage, such as with cysteine, tyrosine and arginine in newborns because of enzymes immaturity (see Table 44-4). Human milk contains both the indispensable and conditionally indispensable amino acids and therefore meets the protein requirements for infants. Breast milk is considered the optimal source of proteins for infants and is the reference amino acid composition by which biologic quality is determined for infants. If a single amino acid in a food protein source is low or absent but is required to support normal metabolism, that specific amino acid becomes the limiting nutrient. For soy-based infant formula, supplementation with the limiting amino acid (methionine) is necessary.

To ensure appropriate growth and to promote satiety, children should consume the recommended amount of protein. Specific recommendations for appropriate dietary protein sources to meet indispensable amino acid requirements are available for groups adopting specific diets, such as vegetarians and vegans. Inclusion of legumes and corn, as well as the use of a variety of food sources to provide all of the required amino acids is a strategy advocated for vegetarians and vegans.

**CARBOHYDRATES**

Carbohydrates are abundant in many foods, including cereals, grains, fruits, and vegetables, and provide approximately 4 kcal/g. Dietary carbohydrates include monosaccharides, which contain 1 sugar molecule (glucose, fructose), disaccharides that contain 2 sugar molecules (sucrose, lactose), oligosaccharides, poly saccharides (which contain multiple sugar molecules in a chain or complex configuration) (starch), and sugar alcohols. Carbohydrates (glucose) serve as an essential energy source for erythrocytes and the central nervous system and a major energy source for all cells. The requirements for carbohydrates are based on the average minimum amount of glucose utilized by the brain. Chronic low carbohydrate intake results in ketosis. Although an UL for carbohydrates has not been set, a maximal intake of <25% or <10% of total energy intake from added sugars has been proposed in various dietary guidelines. Higher intakes of added sugar can displace other macro- and micronutrients and increase risk for nutrient deficiency and excessive energy intake. There is no distinct advantage or benefit obtained from discretionary calorie intake such as that provided by the consumption of added sugars.

The recommended AMDR for carbohydrates (see Table 44-2) were based upon data suggesting a risk for coronary heart disease with diets high in carbohydrates and low in fat. These diets, compared to higher fat intakes, result in high triglycerides, low high-density lipoprotein (HDL) cholesterol, and small LDL cholesterol particles and are associated with a high risk of coronary heart disease, especially in sedentary overweight individuals. Diets within the AMDR for carbohydrates and fats minimize the risks of diabetes, obesity and coronary heart disease. Diets with less than the minimum AMDR for carbohydrate most likely do not meet the AI for fiber (see Table 44-3).

The majority of carbohydrates are present as starches or sugars in food. Simple sugars (mono- and disaccharides) are often added to foods and beverages during food preparation, processing, and packaging to enhance palatability and as preservatives. Non-diet soft drinks, juice drinks, iced tea, and sport drinks are among the major contributors to added sugars in the diet of U.S. children and adolescents. Added sugars increase the risk for obesity, diabetes, and dental caries. Fructose is one such added sugar in the form of high-fructose corn syrup, which is nearly ubiquitous in the U.S. diet. Fructose increases HDL and triglyceride production in the liver and serum uric acid levels which increase systolic blood pressure and is associated with fatty liver disease and metabolic syndrome. Excessive fructose intake, such as in the form of fruit juices, is associated with diarrhea, abdominal pain, and failure to thrive in children.

The **glycemic index** is a measure of the height of blood sugar levels 2 hours following ingestion against the reference standard (a slice of white bread). The glycemic index has predictable effects on blood glucose, hemoglobin A1c, insulin, triglycerides, and HDL cholesterol levels. Lower glycemic index foods are recommended and may reduce the risk of insulin resistance and cardiovascular disease.

**FIBER**

Fiber consists of nondigestible carbohydrates mostly derived from plant sources, such as whole grain, fruits, and vegetables, that escape digestion and reach the colon nearly 100% intact. These compounds were previously classified as being water soluble versus insoluble, which may be a relatively less meaningful distinction, although still commonly used. The DRI classification lists **dietary fiber** (nondigestible carbohydrates and lignin that are intrinsic and intact in plants), **functional fiber** (with known physiologic benefits in humans), and **total fiber** (dietary plus functional).

Although fiber intake does not contribute significantly to energy intake, it does play several important roles. The metabolic fate of fiber is influenced primarily by the colonic bacteria, which depending on the structure of the fiber, can render it susceptible to fermentation (e.g., pectin and oat bran). Common by-products of colonic fermentation include carbon dioxide, methane (in addition to other gases), **oligofructanes** (also known as prebiotics-substrates that nourish beneficial commensurate gastrointestinal microbiota), and **short-chain fatty acids** (SCFAs). The common SCFAs produced by fermentation include acetate, butyrate, and propionate. There is dynamic interplay between the colonic bacterial milieu and the diet. SCFAs influence colonic physiology by stimulating colonic blood flow and fluid and electrolyte uptake. Butyrate is the preferred fuel for the colonicocyte, and it might have a role in maintaining the normal phenotype in these cells.

Dietary fiber might play an important role by diluting toxins, carcinogens, and tumor promoters; by decreasing transit time, thereby decreasing colonic mucosal exposure; and by promoting their expulsion in the fecal stream. Dietary fiber resistant to colonic degradation might also play a role in maintaining and promoting stool bulk and in the regulation of intraluminal pressure and colonic wall resistance, disordered colonic motility, or both. Lack of dietary fiber is associated with constipation and diverticulosis.

All fiber slows gastric emptying and promotes satiety, and thus may help to regulate appetite. Dietary fiber may decrease the rate of release and absorption of simple sugars, and help in the regulation of blood sugar, with lower postprandial blood sugars observed. Dietary fiber has a low glycemic index, and may have a beneficial effect on insulin sensitivity. Fiber also binds luminal cholesterol and reduces absorption and/or enterohepatic circulation of the cholesterol in bile salts (with the intake of more viscous forms of dietary fiber, such as pectin). Soluble fiber types (such as guar gum, oat products, pectin) lower serum cholesterol, while insoluble fiber may reduce serum triglycerides. However, fiber such as psyllium, resistant xtrans, and resistant starch may also have a role in lowering both serum LDL and triglycerides. Decreased fiber intake in Western society has been associated with the increasing incidence and prevalence of diabetes, obesity, cardiovascular disease, colon cancer, and inflammatory bowel disease.

Data are insufficient to establish an EAR for dietary fiber. An AI for dietary fiber has been established based on the intake levels associated with reducing risk for cardiovascular disease and in lowering or normalizing serum cholesterol (see Table 44-3). An UL has not been established for fibers, which are not thought to be harmful to human health. A general rule of thumb used for fiber intake in children is: age (in years) + 5 = grams of fiber intake per day.

**MICRONUTRIENTS**

Vitamins and trace minerals or micronutrients play an essential role in growth and development and contribute to a host of physiologic functions. Many U.S. children have suboptimal intake of iron, zinc, potassium, calcium, vitamin D, and vitamin K, and excess intakes of sodium. Dietary recommendations for micronutrients were originally established to prevent deficiency but also include the impact of micro- nutrients on long-term health outcomes (Table 44-4). Food fortification is an effective strategy to prevent some nutrient deficiencies, and...
Table 44-5  Dietary Reference Intakes for Vitamins

<table>
<thead>
<tr>
<th>NUTRIENT</th>
<th>FUNCTION</th>
<th>LIFE-STAGE GROUP</th>
<th>RDA OR AI</th>
<th>UL</th>
<th>SELECTED FOOD SOURCES</th>
<th>ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION</th>
<th>SPECIAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biotin</td>
<td>Coenzyme in synthesis of fat, glycogen, and amino acids</td>
<td>Infants (µg/day)</td>
<td>0-6 mo</td>
<td>5*</td>
<td>ND</td>
<td>Liver</td>
<td>Smaller amounts in fruits and meats</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7-12 mo</td>
<td>6*</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children (µg/day)</td>
<td>1-3 yr</td>
<td>8*</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4-8 yr</td>
<td>12*</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Males (µg/day)</td>
<td>9-13 yr</td>
<td>20*</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14-18 yr</td>
<td>25*</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19-21 yr</td>
<td>30*</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Females (µg/day)</td>
<td>9-13 yr</td>
<td>20*</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14-18 yr</td>
<td>25*</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19-21 yr</td>
<td>30*</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregnancy (µg/day)</td>
<td>≤18 yr</td>
<td>30*</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19-21 yr</td>
<td>30*</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lactation (µg/day)</td>
<td>≤18 yr</td>
<td>35*</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19-21 yr</td>
<td>35*</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Choline</td>
<td>Precursor for acetylcholine, phospholipids, and betaine</td>
<td>Infants (mg/day)</td>
<td>0-6 mo</td>
<td>125*</td>
<td>ND</td>
<td>Milk, liver, eggs, peanuts</td>
<td>Fishy body odor, sweating, salivation, hypotension, hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7-12 mo</td>
<td>150*</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children (mg/day)</td>
<td>1-3 yr</td>
<td>200*</td>
<td>1,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4-8 yr</td>
<td>250*</td>
<td>1,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Males (mg/day)</td>
<td>9-13 yr</td>
<td>375*</td>
<td>2,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14-18 yr</td>
<td>550*</td>
<td>3,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19-21 yr</td>
<td>550*</td>
<td>3,500</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Females (mg/day)</td>
<td>9-13 yr</td>
<td>375*</td>
<td>2,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14-18 yr</td>
<td>400*</td>
<td>3,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19-21 yr</td>
<td>425*</td>
<td>3,500</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregnancy (mg/day)</td>
<td>≤18 yr</td>
<td>450*</td>
<td>3,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19-21 yr</td>
<td>450*</td>
<td>3,500</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lactation (mg/day)</td>
<td>≤18 yr</td>
<td>550*</td>
<td>3,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19-21 yr</td>
<td>550*</td>
<td>3,500</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Folate aka folic acid, folacin, pteroyl-polyglutamates given as dietary folate equivalents (DFE)**

1 DFE = 1 µg food folate = 0.6 µg folate from fortified food or as a supplement consumed with food = 0.5 µg of a supplement taken on an empty stomach

**Folate Coenzyme in the metabolism of nucleic and amino acids Prevents megaloblastic anemia**

<table>
<thead>
<tr>
<th>Infants (µg/day)</th>
<th>Males (µg/day)</th>
<th>Females (µg/day)</th>
<th>UL for folate (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 mo</td>
<td>7-12 mo</td>
<td>1-3 yr</td>
<td>4-8 yr</td>
</tr>
<tr>
<td>0.6</td>
<td>0.8</td>
<td>1.5</td>
<td>2.0</td>
</tr>
</tbody>
</table>

No adverse effects associated with folate from food or supplements have been reported; this does not mean that there is no potential for adverse effects resulting from high intakes.

**Adverse effects of biotin in humans or animals have been found; this does not mean there is no potential for adverse effects resulting from high intakes.**

Because data on the adverse effects of biotin are limited, caution may be warranted.

**Enriched cereal, grains, dark leafy vegetables, enriched and whole-grain breads and bread products, fortified ready-to-eat cereals**

<table>
<thead>
<tr>
<th>Infants (µg/day)</th>
<th>Males (µg/day)</th>
<th>Females (µg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 mo</td>
<td>7-12 mo</td>
<td>1-3 yr</td>
</tr>
<tr>
<td>0.6</td>
<td>0.8</td>
<td>1.5</td>
</tr>
</tbody>
</table>

**Adverse effects from niacin-containing supplements can include flushing and GI distress**

UL for niacin applies to synthetic forms obtained from supplements and/or fortified foods.

**Niacin**

Includes nicotinic amide, nicotinic acid (pyridine-3 carboxylic acid), and derivatives that exhibit the biologic activity of nicotinamide

Given as niacin equivalents (NE)

1 mg niacin = 60 mg tryptophan

0-6 mo = preformed niacin (not NE)

**Coenzyme or cosubstrate in many biologic reduction and oxidation reactions, thus required for energy metabolism**

<table>
<thead>
<tr>
<th>Infants (mg/day)</th>
<th>Males (mg/day)</th>
<th>Females (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 mo</td>
<td>7-12 mo</td>
<td>1-3 yr</td>
</tr>
<tr>
<td>2*</td>
<td>4*</td>
<td>6</td>
</tr>
</tbody>
</table>

No evidence of adverse effects from consuming naturally occurring niacin in food.

**Meat, fish, poultry, enriched and whole-grain breads and bread products, fortified ready-to-eat cereals**

<table>
<thead>
<tr>
<th>Infants (mg/day)</th>
<th>Males (mg/day)</th>
<th>Females (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 mo</td>
<td>7-12 mo</td>
<td>1-3 yr</td>
</tr>
<tr>
<td>12</td>
<td>20</td>
<td>16</td>
</tr>
</tbody>
</table>

**Adverse effects from niacin-containing supplements can include flushing and GI distress**

UL for niacin applies to synthetic forms obtained from supplements, fortified food, or a combination of these.

**In view of evidence linking poor folate intake with neural tube defects, all women who can become pregnant should consume 400 µg/day from supplements or fortified foods in addition to intake of food folate from a varied diet.**

**Chapter 44**

Nutritional Requirements 275

Continued
### Table 44-5 Dietary Reference Intakes for Vitamins—cont’d

<table>
<thead>
<tr>
<th>NUTRIENT</th>
<th>FUNCTION</th>
<th>LIFE-STAGE GROUP</th>
<th>RDA OR AI</th>
<th>UL</th>
<th>SELECTED FOOD SOURCES</th>
<th>ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION</th>
<th>SPECIAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pantothenic acid</td>
<td>Coenzyme in fatty acid metabolism</td>
<td>Infants (mg/day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0-6 mo</td>
<td>1.7*</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>7-12 mo</td>
<td>1.8*</td>
<td>ND</td>
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<td></td>
<td></td>
<td>Children (mg/day)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-3 yr</td>
<td>2*</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>4-8 yr</td>
<td>3*</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Males (mg/day)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>9-13 yr</td>
<td>4*</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>14-18 yr</td>
<td>5*</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>19-21 yr</td>
<td>5*</td>
<td>ND</td>
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<tr>
<td></td>
<td>Females (mg/day)</td>
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<tr>
<td></td>
<td></td>
<td>9-13 yr</td>
<td>4*</td>
<td>ND</td>
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<tr>
<td></td>
<td></td>
<td>14-18 yr</td>
<td>5*</td>
<td>ND</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>19-21 yr</td>
<td>5*</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pregnancy (mg/day)</td>
<td>≤18 yr</td>
<td>6*</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>19-21 yr</td>
<td>6*</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lactation (mg/day)</td>
<td>≤18 yr</td>
<td>7*</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>19-21 yr</td>
<td>7*</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riboflavin aka vitamin B₂</td>
<td>Coenzyme in numerous redox reactions</td>
<td>Infants (mg/day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0-6 mo</td>
<td>0.3*</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>7-12 mo</td>
<td>0.4*</td>
<td>ND</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Children (mg/day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-3 yr</td>
<td>0.5</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-8 yr</td>
<td>0.6</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Males (mg/day)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>9-13 yr</td>
<td>0.9</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>14-18 yr</td>
<td>1.3</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>19-21 yr</td>
<td>1.3</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Females (mg/day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>9-13 yr</td>
<td>0.9</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>14-18 yr</td>
<td>1.0</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>19-21 yr</td>
<td>1.1</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pregnancy (mg/day)</td>
<td>≤18 yr</td>
<td>1.4</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>19-21 yr</td>
<td>1.4</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lactation (mg/day)</td>
<td>≤18 yr</td>
<td>1.6</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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- No adverse effects associated with pantothenic acid from food or supplements have been reported; this does not mean there is no potential for adverse effects resulting from high intakes
- Because data on adverse effects of pantothenic acid are limited, caution may be warranted
- No adverse effects associated with vitamin B₂ consumption from food or supplements have been reported; this does not mean there is no potential for adverse effects resulting from high intake
- Because data on adverse effects of vitamin B₂ are limited, caution may be warranted
<table>
<thead>
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<th>Nutrient</th>
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<th>Infants (mg/day)</th>
<th>Children (mg/day)</th>
<th>Males (mg/day)</th>
<th>Females (mg/day)</th>
<th>Pregnancy (mg/day)</th>
<th>Lactation (mg/day)</th>
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</table>

**Teratologic effects, liver toxicity (from preformed vitamin A only)**

- Persons with high alcohol intake, pre-existing liver disease, hyperlipidemia, or severe protein malnutrition may be distinctly susceptible to the adverse effects of excess preformed vitamin A intake.
- Beta-carotene supplements are advised only to serve as a provitamin A source for persons at risk for vitamin A deficiency.
<table>
<thead>
<tr>
<th>NUTRIENT</th>
<th>FUNCTION</th>
<th>LIFE-STAGE GROUP</th>
<th>RDA OR AI</th>
<th>UL</th>
<th>SELECTED FOOD SOURCES</th>
<th>ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION</th>
<th>SPECIAL CONSIDERATIONS</th>
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<tbody>
<tr>
<td>Vitamin B&lt;sub&gt;6&lt;/sub&gt;</td>
<td>Coenzyme in the metabolism of amino acids, glycogen, and sphingoid bases</td>
<td>Infants (mg/day)</td>
<td>0-6 mo</td>
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<td>Fortified cereals, organ meats, fortified soy-based meat substitutes</td>
<td>No adverse effects associated with vitamin B&lt;sub&gt;6&lt;/sub&gt; from food have been reported; this does not mean there is no potential for adverse effects resulting from high intake</td>
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<td></td>
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<td></td>
<td></td>
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<td>14-18 yr</td>
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<td></td>
<td></td>
<td>19-21 yr</td>
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<td></td>
<td>Females (mg/day)</td>
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<td></td>
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<td></td>
<td>14-18 yr</td>
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<td>19-21 yr</td>
<td>1.3</td>
<td>100</td>
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<td></td>
<td></td>
<td>Pregnancy (mg/day)</td>
<td>≤18 yr</td>
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<td>19-21 yr</td>
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<td>19-21 yr</td>
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<td>100</td>
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</tr>
<tr>
<td>Vitamin B&lt;sub&gt;12&lt;/sub&gt; aka cobalamin</td>
<td>Coenzyme in nucleic acid metabolism Prevents megaloblastic anemia</td>
<td>Infants (µg/day)</td>
<td>0-6 mo</td>
<td>0.4*</td>
<td>ND</td>
<td>Fortified cereals, meat, fish, poultry</td>
<td>No adverse effects have been associated with consumption of the amounts of vitamin B&lt;sub&gt;12&lt;/sub&gt; normally found in food or supplements; this does not mean there is no potential for adverse effects resulting from high intake</td>
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<td></td>
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<td>0.5*</td>
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<td>Children (µg/day)</td>
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<td>Males (µg/day)</td>
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<td>ND</td>
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<td>Females (µg/day)</td>
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<td>ND</td>
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<td>Lactation (µg/day)</td>
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<td>19-21 yr</td>
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### Vitamin C aka ascorbic acid, dehydroascorbic acid (DHA)

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<th>Infants (mg/day)</th>
<th>Children (mg/day)</th>
<th>Males (mg/day)</th>
<th>Females (mg/day)</th>
<th>Pregnancy (mg/day)</th>
<th>Lactation (mg/day)</th>
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<tbody>
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<td>0-6 mo</td>
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<td>75</td>
<td>65</td>
<td>85</td>
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<td>75</td>
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<td>1,800</td>
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</tr>
<tr>
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<tr>
<td>14-18 yr</td>
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<td>19-21 yr</td>
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</table>

**FUNCTION**
- Cofactor for reactions requiring reduced copper or iron metalloenzyme and as a protective antioxidant

**EXCESSIVE CONSUMPTION**
- No adverse effects associated

Additional information:
- Smokers require additional 35 mg/day of vitamin C over that needed by nonsmokers
- Nonsmokers regularly exposed to tobacco smoke should ensure they meet the RDA for vitamin C

### Vitamin E aka α-tocopherol

α-Tocopherol includes RRR-α-tocopherol, the only form of α-tocopherol that occurs naturally in foods, and the 2R-stereoisomeric forms of α-tocopherol (RRR-, RSR-, RRS-, and RRR-α-tocopherol) that occur in fortified foods and supplements. It does not include the 2S-stereoisomeric forms of α-tocopherol (SRR-, SSR-, SRS-, and SSS-α-tocopherol), also found in fortified foods and supplements.

<table>
<thead>
<tr>
<th>Group</th>
<th>Infants (mg/day)</th>
<th>Children (mg/day)</th>
<th>Males (mg/day)</th>
<th>Females (mg/day)</th>
<th>Pregnancy (mg/day)</th>
<th>Lactation (mg/day)</th>
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<td>15</td>
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<td>1-3 yr</td>
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<td>800</td>
<td></td>
<td>1,000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19-21 yr</td>
<td>1,000</td>
<td></td>
<td>1,000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-6 mo</td>
<td>12</td>
<td></td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-12 mo</td>
<td>19</td>
<td></td>
<td>19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3 yr</td>
<td>15</td>
<td></td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-8 yr</td>
<td>15</td>
<td></td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9-13 yr</td>
<td>800</td>
<td></td>
<td>800</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14-18 yr</td>
<td>800</td>
<td></td>
<td>1,000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19-21 yr</td>
<td>1,000</td>
<td></td>
<td>1,000</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FUNCTION**
- A metabolic function has not yet been identified
- Vitamin E’s major function appears to be as a nonspecific chain-breaking antioxidant

**EXCESSIVE CONSUMPTION**
- No evidence of adverse effects from consuming vitamin E naturally occurring in food
- Adverse effects from vitamin E–containing supplements may include hemorrhagic toxicity
- UL for vitamin E applies to any form of α-tocopherol obtained from supplements, fortified foods, or a combination of these

Additional information:
- Patients on anticoagulant therapy should be monitored when taking vitamin E supplements

**VITAMIN C**
- Citrus fruit, tomatoes, tomato juice, potatoes, Brussels sprouts, cauliflower, broccoli, strawberries, cabbage, spinach
- GI disturbances, kidney stones, excess iron absorption

**VITAMIN E**
- Vegetable oil, unprocessed cereal grains, nuts, fruit, vegetables, meat
- No evidence of adverse effects from consuming vitamin E naturally occurring in food

**EXCESSIVE CONSUMPTION**
- No evidence of adverse effects associated with consumption of vitamin C from food have been reported; this does not mean there is no potential for adverse effects resulting from high intake of vitamin C

**ADDITIONAL INFORMATION**
- Sensory neuropathy has occurred from high intakes of vitamin B6
- Because data on adverse effects of vitamin B6 are limited, caution may be warranted
- Because 10-30% of older people are limited, caution may be warranted
- No adverse effects have been associated with high intake of vitamin B12
- No adverse effects are associated with consumption of vitamin B12 from supplements, fortified foods, or a combination of these
- No adverse effects associated with excessive intake of vitamin B12 from food have been reported; this does not mean there is no potential for adverse effects resulting from high intake of vitamin B12

**RECOMMENDED INTAKES**
- Infants ≤18 yr, 12 µg/day
- Infants 19-21 yr, 15 µg/day
- Children 1-3 yr, 75 µg/day
- Children 4-8 yr, 120 µg/day
- Children 9-13 yr, 150 µg/day
- Children 14-18 yr, 150 µg/day
- Children 19-21 yr, 150 µg/day
- Males ≤18 yr, 120 µg/day
- Males 19-21 yr, 120 µg/day
- Females ≤18 yr, 120 µg/day
- Females 19-21 yr, 120 µg/day
- Pregnancy ≤18 yr, 150 µg/day
- Pregnancy 19-21 yr, 150 µg/day
- Lactation ≤18 yr, 150 µg/day
- Lactation 19-21 yr, 150 µg/day

**UL FOR VITAMIN C**
- Infants ≤18 yr, 12 µg/day
- Infants 19-21 yr, 15 µg/day
- Children 1-3 yr, 75 µg/day
- Children 4-8 yr, 120 µg/day
- Children 9-13 yr, 150 µg/day
- Children 14-18 yr, 150 µg/day
- Children 19-21 yr, 150 µg/day
- Males ≤18 yr, 120 µg/day
- Males 19-21 yr, 120 µg/day
- Females ≤18 yr, 120 µg/day
- Females 19-21 yr, 120 µg/day
- Pregnancy ≤18 yr, 150 µg/day
- Pregnancy 19-21 yr, 150 µg/day
- Lactation ≤18 yr, 150 µg/day
- Lactation 19-21 yr, 150 µg/day

**UL FOR VITAMIN E**
- Infants ≤18 yr, 20 µg/day
- Infants 19-21 yr, 20 µg/day
- Children 1-3 yr, 30 µg/day
- Children 4-8 yr, 50 µg/day
- Children 9-13 yr, 50 µg/day
- Children 14-18 yr, 50 µg/day
- Children 19-21 yr, 50 µg/day
- Males ≤18 yr, 50 µg/day
- Males 19-21 yr, 50 µg/day
- Females ≤18 yr, 50 µg/day
- Females 19-21 yr, 50 µg/day
- Pregnancy ≤18 yr, 50 µg/day
- Pregnancy 19-21 yr, 50 µg/day
- Lactation ≤18 yr, 50 µg/day
- Lactation 19-21 yr, 50 µg/day

**VITAMIN C**
- Patients on anticoagulant therapy should be monitored when taking vitamin E supplements

**VITAMIN E**
- Patients on anticoagulant therapy should be monitored when taking vitamin E supplements

**NUTRIENT GROUP OR AI SOURCES**
- Vitamin C: Citrus fruit, tomatoes, tomato juice, potatoes, Brussels sprouts, cauliflower, broccoli, strawberries, cabbage, spinach
- Vitamin E: Vegetable oil, unprocessed cereal grains, nuts, fruit, vegetables, meat
<table>
<thead>
<tr>
<th>NUTRIENT</th>
<th>FUNCTION</th>
<th>LIFE-STAGE GROUP</th>
<th>RDA OR AI</th>
<th>UL</th>
<th>SELECTED FOOD SOURCES</th>
<th>ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION</th>
<th>SPECIAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K</td>
<td>Coenzyme during the synthesis of many proteins involved in blood clotting and bone metabolism</td>
<td>Infants (µg/day)</td>
<td>0-6 mo</td>
<td>2.0*</td>
<td>ND</td>
<td>Green vegetables (collards, spinach, salad greens, broccoli, Brussels sprouts, cabbage, plant oil, margarine)</td>
<td>No adverse effects associated with vitamin K consumption from food or supplements have been reported in humans or animals; this does not mean there is no potential for adverse effects resulting from high intake</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7-12 mo</td>
<td>2.5*</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children (µg/day)</td>
<td>1-3 yr</td>
<td>30*</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4-8 yr</td>
<td>55*</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Males (µg/day)</td>
<td>9-13 yr</td>
<td>60*</td>
<td>ND</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>14-18 yr</td>
<td>75*</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19-21 yr</td>
<td>120*</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Females (µg/day)</td>
<td>9-13 yr</td>
<td>60*</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14-18 yr</td>
<td>75*</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19-21 yr</td>
<td>90*</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregnancy (µg/day)</td>
<td>≤18 yr</td>
<td>75*</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19-21 yr</td>
<td>90*</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lactation (µg/day)</td>
<td>≤18 yr</td>
<td>75*</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19-21 yr</td>
<td>90*</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Starred numbers are AI, and bold numbers are RDA. RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of 97-98% of members in a group. For healthy breast-fed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all members of the group, but lack of data prevents specifying with confidence the percentage covered by this intake.

UL is the maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Because of a lack of suitable data, ULs could not be established for potassium, water, and inorganic sulfate. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

ND amounts are not determinable because of a lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

* Adequate intake; GI, gastrointestinal; ND, not determinable; PLP, pyridoxal phosphate; PMP, pyridoxamine phosphate; PNP, pyridoxine phosphate; RDA, recommended dietary allowance; UL, upper limit.

has been successfully implemented to prevent iodine and folate deficiency.

Breast milk provides optimal intake of most nutrients including iron and zinc. Although they present in lower amounts than in infant formula, they are more bioavailable and sufficient to meet infant needs until ~4-6 mo of age. After 4-6 mo of age, iron and zinc are required from complementary foods, such as iron-fortified cereal and pureed meats.

**Iron** requirements are higher during infancy and childhood as compared to later life stages, and are higher for menstruating females as compared to males of similar age groups (see Chapter 54). Iron present in animal protein is more bioavailable than that found in vegetables and other foods because it is already incorporated into heme moieties in blood and muscle. Iron deficiency is the most common micronutrient deficiency and is associated with iron-deficiency anemia and neurocognitive deficits. **Zinc** deficiency affects millions of children and is associated with increased risk for impaired linear growth (stunting), impaired immune function, and increased risk for respiratory and diarrheal diseases.

Breast milk is a poor source of **vitamin D** (see Chapter 51). Vitamin D insufficiency is more common than previously thought in infants and children. Vitamin D is central to calcium and bone metabolism, but is also an important determinant of various nonosseous health outcomes. Vitamin D is absorbed in the skin from sunlight and is also present naturally in some foods and fortified in all cow milk products, regardless of fat content, soy milk, almond milk, and orange juice. Sunlight exposure varies by season. Therefore, for populations residing in northern latitudes and/or who have darker skin, sunlight exposure is unlikely to meet the vitamin D needs over the year; in these groups, additional sunlight exposure and/or vitamin D supplementation may be required to achieve optimal status.

Children with darker skin and those who do not consume fortified products should be screened for vitamin D deficiency. The DRI for vitamin D is based on its effects on calcium status and bone health. The goal is to achieve serum levels of 25(OH) D levels above 50 nmol/L (30 ng/dL), which is often achieved using vitamin D supplementation. In 2010, the American Academy of Pediatrics increased total vitamin D intake recommendations to 600 IU/day for infants and children. A supplement was recommended for all breast-fed infants to ensure sufficient intake.

**Calcium** adequacy is determined in part as a function of bone health as measured by bone mineral content and density. The main storage organs for calcium are the bones and teeth. Bone mineral accretion occurs primarily in the pediatric age range, with peak bone mass being achieved by the 2nd to 3rd decade of life. Calcium recommendations vary by age and were also increased from AI to RDA, and the UL was increased in 9-18 yr olds (Table 44-6).

**Vitamin K** is an important determinant of bone health, but is also an important cofactor for coagulation factors (factors II, VII, IX, and X; protein C; and protein S) (see Chapter 53). Status can be assessed by prothrombin time, protein in the absence of vitamin K (PIVKA-II) and the vitamin K–dependent coagulation factor levels. Neonates are at risk for suboptimal vitamin K status, leading to an increased risk for hemorrhagic disease of the newborn. Vitamin K prophylaxis at birth is recommended for all newborn infants.

Potassium and sodium are the main intra- and extracellular cations, respectively, and are involved in transport of fluids and nutrients across the cellular membrane. There is an AI set for **potassium** related to its effects in maintaining a healthy blood pressure, reducing risk for nephrolithiasis, and supporting bone health. Moderate potassium deficiency can occur even in the absence of hypokalemia and can result in increased blood pressure, stroke, and other cardiovascular disease. Most American children have potassium intake below the current recommendations. African-Americans in particular are at increased risk for potassium deficiency. For people at increased risk for hypertension and who are salt sensitive, reducing sodium intake and increasing potassium intake is advised. Leafy green vegetables, vine fruit (such as tomatoes) and root vegetables are good food sources of potassium (see Table 44-6). People with impaired renal function may need to reduce potassium intake as hyperkalemia can increase risk for fatal cardiac arrhythmias among these patients.

**Sodium** has an AI, but given the risk of hypertension, an UL has also been set. The UL threshold may be even lower in African-Americans, who, on average, are more salt sensitive, and for those with hypertension or preexisting renal disease. Dietary sodium intake also displaces potassium intake. Elevated sodium:potassium ratios can increase the risk for nephrolithiasis. Intakes of <2,300 mg (approximately 1 tsp) per day are recommended. The average daily salt intake for most people in the United States and Canada exceeds both the AI and UL. Most of the dietary salt in the United States is found in processed foods, breads, condiments, and as a food preservative, and to enhance palatability. For populations with or at risk for hypertension and renal disease, sodium intake should be decreased to <1,500 mg/day and potassium intake increased to >4,700 mg/day. For persons with hypertension, additional dietary guidelines are available from the Dietary Approaches to Stop Hypertension (DASH) eating plan.

**WATER**

The water requirement and content as a proportion of body weight are highest in infants and decrease with age. Water intake is achieved with liquid and food intake, and losses include excretion in the urine and stool as well as insensible and evaporative losses through the skin and respiratory tract. An AI has been established for water (see Table 44-6). Special considerations are required by life stages and by basal metabolic rate, physical activity, body proportions (surface area to volume), environment, and underlying medical conditions. Breast milk and infant formula provide adequate water, and additional water intake is not required until complementary foods are introduced. Although water contains no calories, the concern is that water intake might actually decrease breast milk intake and displace the intake of essential nutrients during this metabolically very active life stage. The increased fluid needs of infants and young children can be explained in part by the high ratio of body surface area to volume in infancy and high respiratory rate.

The consequences of inadequate fluid intake include dehydration, impaired thermoregulation and heat dissipation, reduced activity tolerance and performance, and reduced intravascular fluid. These deficits can result in an increased compensatory heart rate, hypotension and syncope, and, if uncorrected, renal injury or nephrolithiasis. Excess free water intake is usually better tolerated by healthy adults than by younger children, who may be at increased risk for water intoxication. Hyponatremia can result from excess free water intake coupled with inadequate sodium intake. Fluid intake requirements and restrictions are also influenced by underlying renal and hormonal disorders, including diabetes, the syndrome of inappropriate antidiuretic hormone secretion, and diabetes insipidus.

**MEASURING NUTRITIONAL ADEQUACY**

Growth according to expected patterns can be tracked using the 2000 Centers for Disease Control and Prevention (CDC) and 2006 WHO growth charts (see Chapters 6 and 15). The WHO growth charts are derived from longitudinal and cross-sectional data obtained from a sample of healthy breast-fed infants and children (0-5 yr) who were receiving adequate nutritional intake and medical care from Brazil, Ghana, India, Norway, Oman, and the United States. Consequently, the WHO growth charts are not only descriptive of population average and distribution, but are also prescriptive regarding how adequately nourished healthy children under best-care practices should grow. The CDC and American Academy of Pediatrics recommend the use of the WHO charts to monitor growth of all infants and children (breast and bottle or infant formula fed) from birth to 2 yr of age, and the use of the CDC 2000 growth charts for children 2 to 20 yr of age.

Although the WHO and CDC growth charts are recommended for growth and nutritional assessment, a number of disease-specific charts are available. It is noteworthy that many other disease- or syndrome-specific growth charts are based on small samples of children, and include children with suboptimal nutritional status. For these patient
<table>
<thead>
<tr>
<th>NUTRIENT</th>
<th>FUNCTION</th>
<th>LIFE-STAGE GROUP</th>
<th>AI (mg/day)</th>
<th>UL (mg/day)</th>
<th>SELECTED FOOD SOURCES</th>
<th>ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION</th>
<th>SPECIAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>Maintains fluid volume outside of cells and thus normal cell function</td>
<td>Infants</td>
<td>120</td>
<td>ND</td>
<td>Processed foods with added sodium chloride (salt), benzoate, phosphate; salted</td>
<td>Hypertension</td>
<td>AI is set based on ability to obtain a nutritionally adequate diet for other nutrients and to meet the needs for sweat losses for persons engaged in recommended levels of physical activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0-6 mo</td>
<td>370</td>
<td>ND</td>
<td>meats, bread, nuts, cold cuts; margarine; butter; salt added to foods in cooking or</td>
<td>Increased risk of cardiovascular disease and stroke</td>
<td>Persons engaged in activity at higher levels or in humid climates resulting in excessive sweat might need more than the AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7-12 mo</td>
<td>1,000</td>
<td>1,500</td>
<td>at the table Salt is ~ 40% sodium by weight</td>
<td></td>
<td>UL applies to apparently healthy persons without hypertension; it thus may be too high for persons who already have hypertension or who are under the care of a health professional</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children</td>
<td>1,200</td>
<td>1,900</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-3 yr</td>
<td>1,500</td>
<td>2,200</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-8 yr</td>
<td>1,500</td>
<td>2,300</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Males</td>
<td>2,300</td>
<td>3,600</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>9-13 yr</td>
<td>1,500</td>
<td>2,300</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>14-21 yr</td>
<td>2,300</td>
<td>3,600</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Females</td>
<td>2,300</td>
<td>3,600</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>9-13 yr</td>
<td>1,500</td>
<td>2,300</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>13-21 yr</td>
<td>1,500</td>
<td>2,300</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregnancy and Lactation</td>
<td>1,500</td>
<td>2,300</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥14 yr</td>
<td>1,500</td>
<td>2,300</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloride</td>
<td>With sodium, maintains fluid volume outside of cells and thus normal cell function</td>
<td>Infants</td>
<td>180</td>
<td>ND</td>
<td>Processed foods with added sodium chloride (salt), benzoate, phosphate; salted</td>
<td>In concert with sodium, results in</td>
<td>Chloride is lost, usually with sodium, in sweat, as well as in vomiting and diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0-6 mo</td>
<td>570</td>
<td>ND</td>
<td>meats, nuts, cold cuts; margarine; butter; salt added to foods in cooking or at the</td>
<td>hypertension</td>
<td>AI and UL are equimolar in amount to sodium because most of sodium in diet comes as sodium chloride (salt)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7-12 mo</td>
<td>1,000</td>
<td>1,500</td>
<td>table Salt is ~60% chloride by weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children</td>
<td>1,200</td>
<td>1,900</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-3 yr</td>
<td>1,500</td>
<td>2,300</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-8 yr</td>
<td>1,900</td>
<td>2,900</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Males</td>
<td>2,300</td>
<td>3,400</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>9-13 yr</td>
<td>2,300</td>
<td>3,600</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>14-21 yr</td>
<td>2,300</td>
<td>3,600</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Females</td>
<td>2,300</td>
<td>3,600</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>9-13 yr</td>
<td>2,300</td>
<td>3,600</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>13-21 yr</td>
<td>2,300</td>
<td>3,600</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregnancy and Lactation</td>
<td>2,300</td>
<td>3,600</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥14 yr</td>
<td>2,300</td>
<td>3,600</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>Maintains fluid volume inside/outside of cells and thus normal cell function; acts to blunt the rise of blood pressure in response to excess sodium intake, and decrease markers of bone turnover and recurrence of kidney stones</td>
<td>Infants</td>
<td>400</td>
<td>None set</td>
<td>Fruits and vegetables, dried peas, dairy products, meats, nuts</td>
<td>None documented from food alone, but potassium from supplements or salt substitutes can result in hyperkalemia and possibly sudden death if excess is consumed by persons with chronic renal insufficiency (kidney disease) or diabetes</td>
<td>Persons taking drugs for cardiovascular disease such as ACE inhibitors, ARBs, or potassium-sparing diuretics should be careful not to consume supplements containing potassium and might need to consume less than the AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0-6 mo</td>
<td>700</td>
<td>No UL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>7-12 mo</td>
<td>3,000</td>
<td>No UL</td>
<td></td>
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<td></td>
<td></td>
<td>Children</td>
<td>3,800</td>
<td>No UL</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-3 yr</td>
<td>4,500</td>
<td>No UL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-8 yr</td>
<td>4,700</td>
<td>No UL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Males</td>
<td>4,500</td>
<td>No UL</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>9-13 yr</td>
<td>4,700</td>
<td>No UL</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>14-21 yr</td>
<td>4,700</td>
<td>No UL</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Females</td>
<td>4,700</td>
<td>No UL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>9-13 yr</td>
<td>4,700</td>
<td>No UL</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>13-21 yr</td>
<td>4,700</td>
<td>No UL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregnancy</td>
<td>4,700</td>
<td>No UL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥14 yr</td>
<td>4,700</td>
<td>No UL</td>
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<tr>
<td></td>
<td></td>
<td>Lactation</td>
<td>5,100</td>
<td>No UL</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Vitamin D aka calciferol

1 µg calciferol = 40 IU vitamin D

DRI values are based on absence of adequate exposure to sunlight

<table>
<thead>
<tr>
<th>Group</th>
<th>Infants (µg/day)*</th>
<th>Children (µg/day)*</th>
<th>Males (µg/day)*</th>
<th>Females (µg/day)*</th>
<th>Pregnancy (µg/day)*</th>
<th>Lactation (µg/day)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 mo</td>
<td>10</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>7-12 mo</td>
<td>10</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>1-3 yr</td>
<td>10</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>4-8 yr</td>
<td>10</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
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<tr>
<td>9-21 yr</td>
<td>10</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

#### Vitamin D Functions

- Maintains serum calcium and phosphorus concentrations
- Increases risk of hypertension
- Increased risk of cardiovascular disease such as ACE inhibitors, ARBs, or potassium-sparing diuretics
- Requires additional vitamin D in patients on glucocorticoid therapy

#### Vitamin D Supplements

- Fish liver oils, flesh of fatty fish, liver and fat from seals and polar bears, eggs from hens that have been fed vitamin D, fortified milk products, fortified cereals
- Elevated plasma 25(OH)D concentration causing hypercalcemia

### Calcium

Essential role in blood clotting, muscle contraction, nerve transmission, and bone and tooth formation

<table>
<thead>
<tr>
<th>Group</th>
<th>Infants (µg/day)*</th>
<th>Children (µg/day)*</th>
<th>Males (µg/day)*</th>
<th>Females (µg/day)*</th>
<th>Pregnancy (µg/day)*</th>
<th>Lactation (µg/day)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 mo</td>
<td>200</td>
<td>700</td>
<td>1,300</td>
<td>1,300</td>
<td>1,300</td>
<td>1,300</td>
</tr>
<tr>
<td>7-12 mo</td>
<td>260</td>
<td>1,000</td>
<td>1,000</td>
<td>1,000</td>
<td>1,000</td>
<td>1,000</td>
</tr>
<tr>
<td>1-3 yr</td>
<td>200</td>
<td>700</td>
<td>1,300</td>
<td>1,300</td>
<td>1,300</td>
<td>1,300</td>
</tr>
<tr>
<td>4-8 yr</td>
<td>260</td>
<td>1,000</td>
<td>1,000</td>
<td>1,000</td>
<td>1,000</td>
<td>1,000</td>
</tr>
<tr>
<td>9-18 yr</td>
<td>200</td>
<td>700</td>
<td>1,300</td>
<td>1,300</td>
<td>1,300</td>
<td>1,300</td>
</tr>
<tr>
<td>19-21 yr</td>
<td></td>
<td>1,000</td>
<td>1,000</td>
<td>1,000</td>
<td>1,000</td>
<td>1,000</td>
</tr>
</tbody>
</table>

#### Calcium Functions

- Maintains serum calcium and phosphorus concentrations
- Increases risk of hypertension
- Increases risk of cardiovascular disease such as ACE inhibitors, ARBs, or potassium-sparing diuretics
- Requires additional vitamin D in patients on glucocorticoid therapy

#### Calcium Supplements

- Milk, cheese, yogurt, corn tortillas, calcium-set tofu, Chinese cabbage, kale, broccoli
- Kidney stones, hypercalcemia, milk alkali syndrome, and renal insufficiency
- Amenorrheic women (exercise- or anorexia nervosa-induced) have reduced net calcium absorption

---

*Note: DRI values are based on adequate exposure to sunlight.*
### Table 44-6  Dietary Reference Intakes for Select Micronutrients and Water—cont’d

<table>
<thead>
<tr>
<th>NUTRIENT</th>
<th>FUNCTION</th>
<th>LIFE-STAGE GROUP</th>
<th>AI (mg/day)</th>
<th>UL (mg/day)</th>
<th>SELECTED FOOD SOURCES</th>
<th>ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION</th>
<th>SPECIAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>Critical component of enzymes, cytochromes, myoglobin, and hemoglobin</td>
<td>Infants</td>
<td>0-6 mo</td>
<td>0.27</td>
<td>40</td>
<td>Heme sources: meat, poultry, fish</td>
<td>GI distress</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7-12 mo</td>
<td>11</td>
<td>40</td>
<td></td>
<td>Nonheme sources: dairy, eggs, plant-based foods, breads, cereals, breakfast foods</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children</td>
<td>1-3 yr</td>
<td>7</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-8 yr</td>
<td>10</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Males</td>
<td>9-13 yr</td>
<td>8</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>14-18 yr</td>
<td>11</td>
<td>45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>19-21 yr</td>
<td>8</td>
<td>45</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Females</td>
<td>9-13 yr</td>
<td>8</td>
<td>40</td>
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<td></td>
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<td>14-18 yr</td>
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<td>45</td>
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<td></td>
<td></td>
<td>19-21 yr</td>
<td>18</td>
<td>45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregnancy ≤18 yr</td>
<td>27</td>
<td>45</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>19-21 yr</td>
<td>27</td>
<td>45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lactation ≤18 yr</td>
<td>10</td>
<td>45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>19-21 yr</td>
<td>9</td>
<td>45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zinc</td>
<td>Essential for proper growth and development, and an important catalyst for 100 specific enzymes</td>
<td>Infants</td>
<td>0-6 mo</td>
<td>2</td>
<td>4</td>
<td>Meats, shellfish, legumes, fortified cereals, whole grains</td>
<td>Acutely zinc supplements cause GI irritation and headache; chronic effects of zinc supplementation include impaired immune function, changes in lipoprotein and cholesterol levels, and reduced copper status</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7-12 mo</td>
<td>3</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children</td>
<td>1-3 yr</td>
<td>3</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-8 yr</td>
<td>5</td>
<td>12</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Males</td>
<td>9-13 yr</td>
<td>8</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>14-18 yr</td>
<td>11</td>
<td>34</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>19-21 yr</td>
<td>11</td>
<td>40</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Females</td>
<td>9-13 yr</td>
<td>8</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>14-18 yr</td>
<td>9</td>
<td>34</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>19-21 yr</td>
<td>8</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregnancy ≤18 yr</td>
<td>8</td>
<td>34</td>
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<tr>
<td></td>
<td></td>
<td>19-21 yr</td>
<td>11</td>
<td>40</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lactation ≤18 yr</td>
<td>13</td>
<td>34</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>19-21 yr</td>
<td>12</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td>Maintains homeostasis in the body</td>
<td>Allows transport of nutrients to cells and removal and excretion of waste products of metabolism</td>
<td>Infants (L/day)</td>
<td>Males (L/day)</td>
<td>Females (L/day)</td>
<td>Pregnancy (L/day)</td>
<td>UL (mg/day)</td>
</tr>
<tr>
<td>-------</td>
<td>----------------------------------</td>
<td>----------------------------------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>---------------</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0-6 mo</td>
<td>9-13 yr</td>
<td>18 yr</td>
<td>≥18 yr</td>
<td>None set</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.7</td>
<td>2.4</td>
<td>3.3</td>
<td>2.1</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.8</td>
<td>3.3</td>
<td>3.7</td>
<td>2.1</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.3</td>
<td>2.4</td>
<td>2.3</td>
<td>2.7</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.7</td>
<td>3.3</td>
<td>≥19 yr</td>
<td>≥19 yr</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥19 yr</td>
<td></td>
<td>≥14 yr</td>
<td>3.8</td>
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<td></td>
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</tr>
</tbody>
</table>

**Note:** Bold numbers are RDA. RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of 97-98% of members in a group. For healthy breast-fed infants, the AI is the mean intake. The AI for other life-stage and gender groups is believed to cover the needs of all members of a group, but lack of data prevents specifying with confidence the percentage covered by this intake. UL is the maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Because of a lack of suitable data, ULs could not be established for potassium, water, and inorganic sulfate. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes. ND amounts are not determinable because of a lack of data on adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

ACE, angiotensin-converting enzyme; AI, adequate intake; ARB, angiotensin receptor blocker; GI, gastrointestinal; ND, not determinable; RDA, recommended dietary allowance; UL, upper limit.

groups, disease-specific charts may be helpful to use in conjunction with the WHO or CDC growth charts for comparison to children of similar age and sex from the general population. The goal should be to use this information to approximate growth as closely to that of the general population as possible in these subsets of children, where and when possible. In addition to anthropometry, other nutrient biomarkers can be used to assess status. For infants and children with specific dietary or health concerns, consultation with lactation consultants, registered dieticians, and/or physician nutrition specialists may also be indicated.

Bibliography is available at Expert Consult.
Bibliography
Early nutrition plays an important role in the origin of adult diseases such as type 2 diabetes, hypertension, obesity, and the metabolic syndrome; therefore, appropriate feeding practices should be established in the neonatal period and continued throughout childhood and adolescence to adulthood. Healthy feeding in children requires partnerships between family members, the healthcare system, schools, the community, and the government.

FEEDING DURING THE FIRST YEAR OF LIFE

Breastfeeding

The American Academy of Pediatrics (AAP) and World Health Organization (WHO) have declared breastfeeding and the administration of human milk to be the normative practice for infant feeding and nutrition. Breastfeeding has documented short- and long-term medical and neurodevelopmental advantages (Tables 45-1 and 45-2) and rare contraindications (Table 45-3). Thus the decision to breastfeed should be considered a public health issue and not only a lifestyle choice. The AAP and the WHO recommend that infants should be exclusively breastfed or given breast milk for 6 months. Breastfeeding should be continued with the introduction of complementary foods for 1 year or longer, as mutually desired by mother and infant. The success of breastfeeding initiation and continuation depends on multiple factors, such as type 2 diabetes, hypertension, obesity, and the metabolic syndrome; therefore, appropriate feeding practices should be established in the neonatal period and continued throughout childhood and adolescence to adulthood. Healthy feeding in children requires partnerships between family members, the healthcare system, schools, the community, and the government.

knowledge of breastfeeding. As part of the discharge teaching process, issues surrounding infant feeding, elimination patterns, breast engorgement, basic breast care, and maternal nutrition should be discussed. A follow-up appointment is recommended within 24-48 hr after hospital discharge.

Nipple Pain

Nipple pain is one of the most common complaints of breastfeeding mothers in the immediate postpartum period. Poor infant positioning and improper latch are the most common reasons for nipple pain beyond the mild discomfort felt early in breastfeeding. If the problem persists and the infant refuses to feed, consideration needs to be given to nipple candidiasis. If present the mother should be treated with an antifungal cream that is wiped away before feeding, and the infant persists and the infant refuses to feed, consideration needs to be given to nipple candidiasis. If present the mother should be treated with an antifungal cream that is wiped away before feeding, and the infant treated with oral medication.

Engorgement

In the second stage of lactogenesis, physiologic fullness of the breast occurs. Breasts may become engorged: firm, overfilled, and painful as the pattern and volume of milk production is adjusting to the infant's feeding schedule. Incomplete removal of milk as a result of poor breastfeeding technique or infant illness can cause engorgement. Breastfeeding immediately at signs of infant hunger will eventually prevent this

Table 45-1  Selected Beneficial Properties of Human Milk Compared to Infant Formula

<table>
<thead>
<tr>
<th>Secretory IgA</th>
<th>Specific antigen-targeted antiinfective action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactoferrin</td>
<td>Immunomodulation, iron chelation, antimicrobial action, antiadhesive, trophic for intestinal growth</td>
</tr>
<tr>
<td>κ-Casein</td>
<td>Antiadhesive, bacterial flora</td>
</tr>
<tr>
<td>Oligosaccharides</td>
<td>Prevention of bacterial attachment</td>
</tr>
<tr>
<td>Cytokines</td>
<td>Antinflammatory, epithelial barrier function</td>
</tr>
<tr>
<td>Growth factors</td>
<td></td>
</tr>
<tr>
<td>Epidermal growth factor</td>
<td>Luminal surveillance, repair of intestine</td>
</tr>
<tr>
<td>Transforming growth factor (TGF)</td>
<td>Promotes epithelial cell growth (TGF-β)</td>
</tr>
<tr>
<td>Nerve growth factor</td>
<td>Promotes neural growth</td>
</tr>
<tr>
<td>Enzymes</td>
<td></td>
</tr>
<tr>
<td>Platelet-activating factor-acetylhydrolase</td>
<td>Blocks action of platelet-activating factor</td>
</tr>
<tr>
<td>Glutathione peroxidase</td>
<td>Prevents lipid oxidation</td>
</tr>
<tr>
<td>Nucleotides</td>
<td>Enhance antibody responses, bacterial flora</td>
</tr>
</tbody>
</table>


Table 45-2  Conditions for Which Human Milk Has Been Suggested to Possibly Have a Protective Effect

| Acute disorders | Crohn disease |
| Diarrhea | Childhood cancer |
| Otis media | Lymphoma |
| Urinary tract infection | Leukemia |
| Necrotizing enterocolitis | Recurrent otitis media |
| Septicemia | Allergy |
| Infant botulism | Obesity and overweight |
| Insulin-dependent diabetes mellitus | Hospitalizations |
| Celiac disease | Infant mortality |

Chapter 45

Feeding Healthy Infants, Children, and Adolescents

Elizabeth P. Parks, Ala Shaikhkhalil, Veronique Groleau, Danielle Wendel, and Virginia A. Stallings
from occurring. To reduce engorgement, breasts should be softened prior to infant feeding with a combination of hot compresses and expression of milk. Between feedings a supportive bra should be worn, cold compresses applied, and oral nonsteroidal antiinflammatory medications administered.

**Mastitis**

Mastitis occurs in 2-3% of lactating women and is usually unilateral, manifesting with localized warmth, tenderness, edema, and erythema after the second postdelivery week. Sudden onset of breast pain, myalgia, and fever with fatigue, nausea, vomiting, and headache can also occur. Organisms implicated in mastitis include *Staphylococcus aureus*, *Escherichia coli*, group A streptococcus, *Haemophilus influenzae*, *Klebsiella pneumoniae*, and *Bacteroides* spp. Diagnosis is confirmed by physical examination. Oral antibiotics and analgesics, while promoting breastfeeding or emptying of the affected breast, usually resolve the infection. A breast abscess is a less common complication of mastitis, but it is a more serious infection that requires intravenous antibiotics, incision, and drainage, along with temporary cessation of feeding from that breast.

---

**Inadequate Milk Intake**

Insufficient milk intake, dehydration, and jaundice in the infant can become evident within the first week of life. Signs of insufficient milk intake include: lethargy, delayed stooling, decreased urine output, weight loss >7% of birth weight, hypernatremic dehydration, inconsolable crying and increased hunger. Insufficient milk intake may be caused by insufficient milk production, failure of established breastfeeding, and health conditions in the infant that prevent proper breast stimulation. Parents should be counseled that breastfed neonates feed 8-12 times a day with a minimum of 8 times per day. Careful attention to prenatal history can identify maternal factors that may be associated with this problem (failure of breasts to enlarge during pregnancy or within the first few days after delivery). Direct observation of breastfeeding can help identify improper technique. If a large volume of milk is expressed manually after breastfeeding, then the infant might not be extracting enough milk, eventually leading to decreased milk output. Late preterm infants (34-36 wk) are at risk for insufficient milk syndrome because of poor suck and swallow patterns or medical issues.

**Jaundice**

Breastfeeding jaundice is a common reason for hospital readmission of healthy breastfed infants and is largely related to insufficient fluid...
intake during the first week of life (see Chapter 102.3). It may also be associated with dehydration and hypernatremia. Breast milk jaundice is a different disorder that causes persistently high serum indirect bilirubin in a thriving healthy baby that becomes evident later than breastfeeding jaundice, but which generally declines in the 2nd to 3rd wk of life. Infants with severe or persistent jaundice should be evaluated for other medical causes (see Chapter 102.3) before ascribing the jaundice to breast milk that might contain inhibitors of glucuronyl transferase or enhanced absorption of bilirubin from the gut. Persistently high bilirubin levels may require changing from breast milk to infant formula for 24-48 hr and/or treatment with phototherapy without cessation of breastfeeding. Breastfeeding should resume after the decline in serum bilirubin. Parents should be reassured and encouraged to continue collecting breast milk during the period when the infant is taking formula.

Collecting Breast Milk
The pumping of breast milk is a common practice when the mother and baby are separated for work, illness, or hospitalization of mother or infant. Good hand washing and hygiene should be emphasized. Electric breast pumps are more efficient and better tolerated by mothers than mechanical pumps or manual expression. Collection kits should be cleaned with hot soapy water, rinsed, and air dried after each use. Glass or plastic containers should be used to collect the milk, and milk should be refrigerated and then used within 48 hr. Expressed breast milk can be frozen and used for up to 6 mo. Milk should be thawed rapidly by holding under running tepid water and used completely within 24 hr after thawing. Milk should never be microwaved.

Growth of the Breastfed Infant
The rate of weight gain of the breastfed infant differs from that of the formula-fed infant, and the infant's risk for excess weight gain during late infancy may be associated with bottle feeding. The WHO growth charts are based on the growth of healthy breastfed infants through the 1st yr of life. These standards (http://www.who.int/childgrowth) are the result of a study in which >8,000 children were selected from 6 countries. The infants were selected based on healthy feeding practices (breastfeeding), good health care, high socioeconomic status, and non-smoking mothers, so that they reflect the growth of breastfed infants in the optimal conditions and can be used as prescriptive rather than normative curves. Charts are available for growth monitoring from birth to age 6 yr. The Centers for Disease Control and Prevention (CDC) recommends use of the WHO growth charts for infants 0-23 months of age, and CDC growth charts for ages 24 mo to 20 yr.

Formula Feeding (Fig. 45-1)
Despite efforts to promote exclusive breastfeeding through 6 months, less than 50% of women continue to breastfeed at 6 months. Most women make their infant feeding choices early in pregnancy. Parental preference is the most common reason for using infant formula. However, infant formula is also indicated in infants whose intake of breast milk is contraindicated for infant factors (e.g., inborn errors of metabolism), and maternal factors (see Table 45-3). In addition infant formula is used as a supplement to support inadequate weight gain in breastfed infants.

Infant formulas marketed in the United States are safe and nutritionally adequate as the sole source of nutrition for healthy infants for the first 6 months of life. Infant formulas are available in ready-to-feed, concentrated liquid or powder forms. Ready-to-feed products generally provide 20 kcal/30 mL (1 oz) and approximately 67 kcal/dL. Concentrated liquid products, when diluted according to instructions, provide a preparation with the same concentration. Powder formulas come in single or multiple servings and when mixed according to instructions will result in similar caloric density.

Although infant formulas are manufactured in adherence to good manufacturing practices and are regulated by the U.S. Food and Drug Administration (FDA), there are still potential safety issues. Powder preparations are not sterile, and although the number of bacterial colony-forming units per gram of formula is generally lower than allowable limits, outbreaks of infections with Enterobacter sakazakii have been documented, especially in premature infants. The powder preparations can contain other coliform bacteria but have not been linked to disease in healthy term infants. Care must be taken in following the mixing instructions to avoid over- or underdilution, to use boiled or sterilized water, and to use the specific scoops provided by the manufacturer as scoop sizes vary. Water that has been boiled should be allowed to cool fully to prevent degradation of heat labile nutrients, specifically vitamin C. Well water should be tested regularly for bacteria and toxin contamination. Municipal water can contain variable concentrations of fluoride, and if the concentrations are high, bottled water that is defluoridated should be used to avoid toxicity.

Parents should be instructed to use proper handwashing techniques when preparing formula and feedings for the infant. Guidance to follow written instructions for storage should also be given. Once opened, ready-to-feed and concentrated liquid containers can be covered with aluminum foil or plastic wrap and stored in the refrigerator for no longer than 48 hr. Powder formula should be stored in a cool, dry place; once opened, cans should be covered with the original plastic cap or aluminum foil, and the powdered product can be used within 4 weeks. Once prepared, all bottles regardless of type of formula should be used within 24 hours. Formula should be used within 2 hours of removal from the refrigerator and once a feeding has started, that formula should be used within an hour or be discarded. Prepared formula stored in the refrigerator should be warmed by placing the container in warm water for ~5 min. Formula should not be heated in a microwave, because it can heat unevenly and result in burns despite appearing to be at the right temperature when tested.

Formula feedings should be ad libitum, with the goal of achieving growth and development to the child’s genetic potential. The usual intake to allow a weight gain of 25-30 g/day will be 140-200 mL/kg/day in the first 3 months of life. The rate of weight gain declines from 3-12 months of age.

COW MILK PROTEIN–BASED FORMULAS
Intact cow milk–based formulas in the United States contain a protein concentration varying from 1.8 to 3 g/100 kcal or (1.45-1.6 g/dL), considerably higher than in mature breast milk (1.5 g/100 kcal). This increased concentration is designed to meet the needs of the youngest infants but leads to excess protein intake for older infants. In contrast, breastfed infants receive protein intakes that match their needs at various ages. The whey:casein ratio varies from 18:82 to 60:40; one manufacturer markets a formula that is 100% whey. The predominant whey protein is β-globulin in cow milk and α-lactalbumin in human milk. This and other differences between human milk and cow milk–based formulas result in different plasma amino acid profiles in infants on different feeding patterns, but a clinical significance of these differences has not been demonstrated.

Plant or a mixture of plant and animal oils are the source of fat in infant formulas; fat provides 40-50% of the energy in cow milk–based formulas. Fat blends are better absorbed than dairy fat and provide saturated, monounsaturated, and polyunsaturated fatty acids (PUFAs). All infant formulas are supplemented with long-chain PUFAs, docosahexaenoic acid (DHA), and arachidonic acid (ARA) at varying

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### Table 45-5 Patterns of Milk Supply

<table>
<thead>
<tr>
<th>DAY OF LIFE</th>
<th>MILK SUPPLY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Some milk (~5 mL) may be expressed</td>
</tr>
<tr>
<td>Days 2-4</td>
<td>Lactogenesis, milk production increases</td>
</tr>
<tr>
<td>Day 5</td>
<td>Milk present, fullness, leaking felt</td>
</tr>
<tr>
<td>Day 6 onward</td>
<td>Breasts should feel “empty” after feeding</td>
</tr>
</tbody>
</table>

concentrations. ARA and DHA are found at varying concentrations in human milk and vary by geographic region and maternal diet. No studies in term infants have found a negative effect of DHA and ARA supplementation, and some studies have demonstrated positive effects on visual acuity and neurocognitive development. A critical review concluded that there are no consistent effects of long-chain PUFAs on visual acuity in term infants. A Cochrane review concluded that routine supplementation of milk formula with long chain PUFAs to improve the physical, neurodevelopmental, or visual outcomes of term infants cannot be recommended based on the current evidence. DHA and ARA are derived from single-cell microfungi and microalgae and are classified as generally recognized as safe for use in infant formulas at approved concentrations and ratios.

Lactose is the major carbohydrate in breast milk and in standard cow milk–based formulas for term infants. Formulas for term infants may also contain modified starch or other complex carbohydrates. Carbohydrates comprise 69-75g/L of cow milk–based formula.

SOY FORMULAS
Soy protein–based formulas on the market are all free of cow milk–based protein and lactose and use sucrose, corn syrup solids, and/or maltodextrin to provide 67 kcal/dL. They meet the vitamin, mineral, and electrolyte guidelines from the AAP and the FDA for feeding term infants. The protein is a soy isolate supplemented with L-methionine, L-carnitine, and taurine to provide a protein content of 2.45-2.8 g per 100 kcal or 1.7-1.8 g/dL.

The quantity of specific fats varies by manufacturer and is usually similar to the manufacturer's corresponding cow milk–based formula. The fat content is 5.0-5.5 g per 100 kcal or 3.4-3.6 g/dL. The oils used in both cow milk and soy formula include soy, palm, sunflower, olein, safflower, and coconut. DHA and ARA are also added.

In term infants, although soy protein–based formulas have been used to provide nutrition resulting in normal growth patterns, there are few indications for use in place of cow milk–based formula. Indications for soy formula include galactosemia and hereditary lactase deficiency, because soy–based formulas are lactose–free; and situations in which a vegetarian diet is preferred. Most healthy infants with acute gastroenteritis can be managed after rehydration with continued use of breast milk or cow–based formulas and do not require a lactose–free formula, such as soy–based formula. However, soy protein–based formulas may be indicated when documented secondary lactose intolerance occurs. Soy protein–based formulas have no advantage over cow protein–based formulas as a supplement for the breastfed infant, unless the infant has one of the indications noted previously and are not recommended for preterm infants. The routine use of soy protein–based formula has no proven value in the prevention or management of infantile colic, fussiness, or atopic disease. Infants with documented cow protein–induced enteropathy or enterocolitis often are also sensitive to soy protein and should not be given isolated soy protein–based formula. They should be provided formula derived from extensively hydrolyzed protein or synthetic amino acids. Soy formulas contain phytoestrogens, which have been shown to have physiologic activity in rodent models but a meta-analysis of the topic done by the Center for the Evaluation of Risks to Human Reproduction concluded that there is minimal concern for adverse developmental effects in infants fed soy formula.

PROTEIN HYDROLYSATE FORMULA
Protein hydrolysate formulas may be partially hydrolyzed, containing oligopeptides with a molecular weight of <5000 Da, or extensively hydrolyzed, containing peptides with a molecular weight <3000 Da. Partially hydrolyzed proteins have fat blends similar to cow milk–based formulas, and carbohydrates are supplied by corn maltodextrin or corn syrup solids. Because the protein is not extensively hydrolyzed, these formulas should not be fed to infants who are allergic to cow protein. In studies of formula fed infants who are at high risk of developing...
atopic disease there is modest evidence that childhood atopic dermatitis may be delayed or prevented by the use of extensively or partially hydrolyzed formulas, compared with cow milk–based formula. Comparative studies of the various hydrolyzed formulas have also indicated that not all formulas have the same protective benefit. Extensively hydrolyzed formulas may be more effective than partially hydrolyzed in preventing atopic disease. Extensively hydrolyzed formulas are recommended for infants intolerant to cow milk or soy proteins. These formulas are lactose free and can include medium-chain triglycerides, making them useful in infants with gastrointestinal malabsorption as a consequence of cystic fibrosis, short gut syndrome, prolonged diarrhea, and hepatobiliary disease.

AMINO ACID FORMULAS
Amino acid formulas are peptide-free formulas that contain mixtures of essential and nonessential amino acids. They are designed for infants with dairy protein allergy who failed to thrive on extensively hydrolyzed protein formulas. The effectiveness of amino acid formulas to prevent atopic disease has not been studied.

Milk and Other Fluids
Neither breastfed nor formula-fed infants require additional water unless dictated by high environmental temperature. Vomiting and spitting up are common in infants. When weight gain and general well-being are noted, no change in formula is necessary.

Whole cow milk should not be introduced until 12 mo of age. In children between 12 and 24 mo of age for whom being overweight or obesity is a concern or who have a family history of obesity, dyslipidemia, or cardiovascular disease, the use of reduced-fat milk is appropriate. Otherwise whole milk is recommended until age 24 months changing to 2% at 24 months, and 1% at 3 yr of age for healthy children. Regardless of the type, all milk consumed should be pasteurized.

Infants and young children are particularly susceptible to infections such as E. coli, Campylobacter, and Salmonella found in raw or unpasteurized milk. For cultural and other reasons, such as parental preference, goat milk is sometimes given in place of formula although this is not recommended. Goat milk has been shown to cause significant electrolyte disturbances and anemia because it has low folic acid concentrations.

COMPLEMENTARY FEEDING
The timely introduction of complementary foods (solid and liquid foods other than breast milk or formula, also called weaning foods or beikost) during infancy is necessary to enable transition from milk feedings to other table foods and is important for nutritional and developmental reasons (Table 45-6). The ability of exclusive breastfeeding to meet macronutrient and micronutrient requirements becomes limiting with increasing age of the infant. The recommendation for timing of complementary feed initiation is based on the benefits on neurodevelopment and prevention of future comorbidities (see Table 45-2) from exclusive breastfeeding for 6 months. The AAP, WHO, and European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition all recommend exclusive breastfeeding for the first 6 months. Similar data on the benefits of the exclusive use of formula for 6 months have not been published.

Some complementary foods are more nutritionally appropriate than others to complement breast milk or infant formula. The food consumption patterns of U.S. infants and toddlers demonstrate that nearly all infants ≤12 mo consumed some form of milk every day; infants >4 mo consumed more formula than human milk, and by 9-11 mo of age 20% consumed whole cow milk and 25% consumed nonfat or reduced-fat milk.

The most commonly fed complementary foods between 4 and 11 mo of age are infant cereals. Nearly 45% of infants between 9 and 11 mo of age consumed noninfant cereals. Infant eating patterns also vary, with up to 61% of infants 4-11 mo of age consuming no vegetables. Among those who consumed vegetables, French fries were the most common vegetables in toddlers. Positive changes in the last decade include increased duration of breastfeeding, delayed introduction of complementary foods, and decreased juice consumption. Continuing concerns included lack of fruits and vegetables, diets low in iron, essential fatty acids, fiber and whole grains, and high in saturated fat and sodium. Table 45-6 summarizes the AAP recommendations for initiating complementary foods.

The complementary foods should be varied to ensure adequate macro- and micronutrient intake. In addition to complementary foods introduced at 6 mo of age, continued breastfeeding or the use of infant formula for the entire 1st year of life should be encouraged. Overconsumption of energy-dense complementary foods can lead to excessive weight gain in infancy, resulting in an increased risk of obesity in childhood.

FEEDING TODDLERS AND PRESCHOOL-AGE CHILDREN
Toddlerhood is a period when eating behavior and healthful habits can be established and is often a confusing and anxiety-generating period. Growth after the 1st yr slows, motor activity increases, and appetite decreases. Birth weight triples during the 1st year of life and quadruples by 2 yr of age, reflecting this slowing in growth velocity. Eating behavior is erratic, and the child appears distracted as the child explores the environment. Children consume a limited variety of foods and often only “like” a particular food for a period of time and then reject the favored food. The use of growth charts to demonstrate adequate growth and to provide guidance about typical behavior and eating habits will help allay concerns of parents. Important goals of early childhood nutrition are to foster healthful eating habits and to offer foods that are developmentally appropriate.

Feeding Practices
The period starting after 6 mo until 15 mo is characterized by the acquisition of self-feeding skills because the infant can grasp finger foods, learn to use a spoon, and eat soft foods (Table 45-7). Around 12 mo of age, the child learns to drink from a cup and may still breastfeed or desire formula bottle feeding. Bottle weaning should begin around 12-15 mo and bedtime bottles should be discouraged because of the association with dental carries. Unless being used at mealtime, the sippy cup should only contain water to prevent caries. Sugar-sweetened beverages and 100% fruit juice should also be discouraged from being used in bottles in all infants at all times. Cups without a lid can be used for no more than 4-6 oz/day of 100% fruit juice for toddlers. In the 2nd year of life, self-feeding becomes a norm and provides the opportunity for the family to eat together with less stress. Self-feeding allows the child to limit the child’s intake. Child feeding is an interactive process. Children receive cues regarding appropriate feeding behaviors from parents. Parents should ignore negative eating behaviors unless the behavior jeopardizes the health and safety of the child. In addition, parents should eat with their

<table>
<thead>
<tr>
<th>Table 45-6</th>
<th>Important Principles for Weaning</th>
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<tbody>
<tr>
<td><strong>Begin at 6 mo of age</strong></td>
<td>Begin at 6 mo of age, encourage a cup rather than a bottle.</td>
</tr>
<tr>
<td>At the proper age, encourage a cup rather than a bottle</td>
<td>Introduce 1 food at a time.</td>
</tr>
<tr>
<td>Energy density should exceed that of breast milk</td>
<td>Iron-containing foods (meat, iron-supplemented cereals) are required.</td>
</tr>
<tr>
<td>Zinc intake should be encouraged with foods such as meat, dairy products, wheat, and rice</td>
<td>Phytate intake should be low to enhance mineral absorption.</td>
</tr>
<tr>
<td>Breast milk should continue to 12 mo, formula or cow milk is then substituted</td>
<td>Give no more than 24 oz/day of cow milk.</td>
</tr>
<tr>
<td>Fluids other than breast milk, formula, and water should be discouraged</td>
<td>Give no more than 4-6 oz/day of fruit juices; no sugar-sweetened beverages.</td>
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</table>

of the food offered and the level of supervision during meals. Parents are encouraged to assess the quality of the food served at daycare by asking questions, visiting the center, and taking part in parent committees. Free or reduced-price snacks and meals are provided in daycare centers for low- and medium-income communities through the U.S. Department of Agriculture (USDA) Child and Adult Care Food Program. Participating programs are required to provide meals and snacks that meet the meal regulations set by the USDA, guaranteeing a certain level of food quality. However, often for monetary reasons, many daycare centers still struggle to provide high-quality meals and snacks.

**FEEDING SCHOOL-AGE CHILDREN AND ADOLESCENTS**

**MyPlate**

The USDA MyPlate (www.choosemyplate.gov) is a basis for building an optimal diet for children and adults (Fig. 45-2). MyPlate is based on the Dietary Guidelines for Americans, 2010 and replaces MyPyramid. MyPlate is aimed at the general public to provide a visual representation of the different food groups and their portion sizes. In addition to food group information, the website provides discretionary calorie information. It provides weight management strategies, and abilities to track calories and physical activity goals. A personalized eating plan based on these guidelines provide, on average over a few days, all the essential nutrients necessary for health and growth, while limiting nutrients associated with chronic disease development. MyPlate can also be used as an Internet interactive tool that allows customization of recommendations, based on age, sex, physical activity, and, for some populations, weight and height. Print material is also available for families without Internet access.

Recommendations based on MyPlate emphasize making half the plate vegetables and fruit, one half of the plate protein and grains, with protein having the smallest section. Protein replaces the meat category as many protein sources are not from animals. A separate dairy section is included. Physical activity recommendations to achieve a healthful energy balance are not visually displayed, but are provided on the website. MyPlate has removed foods that have low nutritional value, such as sweetened sugar beverages, and sweetened bakery products.

In the United States and in an increasing number of other countries, the vast majority of children and adolescents do not consume a diet that follows the recommendations of MyPlate. The intake of...
discretionary calories is much higher than recommended, with frequent consumption of sweetened sugar beverages (soda, juice drinks, iced tea, sport drinks), snack foods, high-fat meat (bacon, sausage), and high-fat dairy products (cheese, ice cream). Intake of dark green and orange vegetables (as opposed to fried white potatoes), whole fruits, reduced-fat dairy products, and whole grain is typically lower than recommended. Furthermore, unhealthful eating habits such as larger-than-recommended portion sizes; food preparation that adds fat, sugar, or salt; skipping breakfast and/or lunch; grazing; or following fad diets is prevalent and associated with a poorer diet quality. MyPlate offers a helpful and customer-friendly tool to assist pediatricians counseling families on optimal eating plans for short- and long-term health.

**Eating at Home**

At home, much of what children and adolescents eat is under the control of their parents. Typically, parents shop for groceries and they control, to some extent, what food is available in the house. It has been demonstrated that modeling of healthful eating behavior by parents is a critical determinant of the food choices of children and adolescents. Counseling to improve diet should include guiding parents in using their influence to make healthier food choices available and attractive at home.

Regular family meals sitting at a table, as opposed to eating alone, in the living room, or watching television/screens, are associated with improved diet quality, perhaps because of increased opportunities for positive parenting during meals. Such an ideal situation is recommended but a challenge for many families who, with busy schedules and other stressors, are unable to provide such a setting. Another parenting challenge is to control the excess appetite of some children and adolescents. Encourage children to eat at a slower pace and to chew their food properly. Encourage conversation at the dinner table to prolong eating to 15 minutes. Offering vegetables while children are hungry at the beginning of the meal has been shown to increase vegetable consumption. Useful strategies, when the child is still hungry after a meal, include a 15- to 20-min pause (allow child to engage in another activity) before a second serving or offering foods that are insufficiently consumed, such as vegetables, whole grains, or fruits.

**Eating at School**

The National School Lunch Program and the School Breakfast Program provide low-cost meals to more than 5 billion children nationwide. Guidelines for meals are taken from the *Dietary Guidelines for Americans and the Dietary Reference, 2005*. Recommendations regarding the use of age-grade portion sizes, and amounts of vegetable and fruits, grains, and fats were included (Table 45-8). The training and equipment for school food service staff, school community engagement, parent education, and food industry involvement are among the necessary components. The year 2020 is the target year for achieving recommendations for sodium. In the meantime, while schools are working on implementing changes, parents should be encouraged to examine the weekly menu with their child and assist with their choices ahead of time. If children bring their lunch from home recommendations for what constitutes a healthy lunch should be provided by the Pediatrician. Parents can be directed to [www.choosemyplate.org](http://www.choosemyplate.org) for healthy lunch ideas. In addition parties within classrooms should be limited to once a month.

**Eating Out**

The number of meals eaten outside the home or brought home from takeout restaurants has increased in all age groups of the U.S. population. The increased convenience of this meal pattern is undermined by the generally lower nutritional value of the meals, compared to home-cooked meals. Typically, meals consumed or purchased in fast-food or casual restaurants are of large portion size, are dense in calories, and contain large amounts of saturated fat, salt, and sugar, and low amounts of whole grains, fruits, and vegetables. Although still a problem currently, trans fat is slowing being phased out of most commercial restaurants. Although an increasing number of restaurants offer healthier alternatives, the vast majority of what is consumed at restaurants does not fit MyPlate.

With increasing age, an increasing number of meals and snacks are also consumed during peer social gatherings at friends’ houses and parties. When a large part of a child’s or adolescent’s diet is consumed on these occasions, the diet quality can suffer, because food offerings are typically of low nutritional value. Parents and pediatricians need to guide teens in navigating these occasions while maintaining a healthful diet and enjoying meaningful social interactions. These occasions often are also opportunities for teens to consume alcohol; consequently, adult supervision is important.

**NUTRITION ISSUES OF IMPORTANCE ACROSS PEDIATRIC AGES**

**Food Environment**

Most families have some knowledge of nutrition and intend to provide their children with a healthful diet. The discrepancy between this fact and the actual quality of the diet consumed by U.S. children is often explained by challenges in the environment for families to make healthful food choices. Because the final food choice is made by individuals, children or their parents, interventions to improve diet have focused on individual knowledge and behavior changes, but have had limited success. A main determinant of food choice is taste, but other factors also influence these choices. One of the most useful conceptual frameworks for understanding the child’s food environment in the context of obesity illustrates the variety of individual food and physical activity choices. Many of these determinants are not under the direct control of individual children or parents (Fig. 45-3). Understanding the context of food and lifestyle choices helps in understanding lack of changes or “poor compliance” and can decrease the frustration often experienced by the pediatricians who might “blame the victims” for behavior that is not entirely under their control.

Marketing and advertising of food to children is a particularly illustrative aspect of the food environment. Marketing includes strategies as diverse as shelf placements, association of cartoon characters with food products, coupons, and special offers or pricing, all of which influence food purchase choices. Television advertising is an important part of how children and adolescents hear about food, with an estimated 40,000 TV commercials per yr, seen by the average U.S. child, many of which are for food, as compared to the few hours of nutrition education they receive in school. Additional food advertisement increasingly occurs as brand placement in movies and TV shows, on websites, and even video games.

<table>
<thead>
<tr>
<th>Table 45-8 Revised National School Lunch Program and School Breakfast Program Recommendations</th>
</tr>
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<tbody>
<tr>
<td>• Portion sizes of food are to be based on age-grade groups</td>
</tr>
<tr>
<td>• School lunches and breakfasts will have a minimum and maximum calorie level, maximum saturated fat content, and a maximum sodium content</td>
</tr>
<tr>
<td>• Foods must contain zero grams of trans fat per serving</td>
</tr>
<tr>
<td>• The inclusion of unsaturated vegetable oils is encouraged within calorie limits</td>
</tr>
<tr>
<td>• Vegetables and fruits are not interchangeable</td>
</tr>
<tr>
<td>• Vegetable offerings at lunch must include ½ cup equivalent of the following: dark green vegetables, bright orange vegetables, and legumes</td>
</tr>
<tr>
<td>• No more than half of fruit servings may be in the form of juice</td>
</tr>
<tr>
<td>• At least ½ of bread/grain offered must be whole grain</td>
</tr>
<tr>
<td>• Milk must be fat-free if flavored and either fat free or 1% if plain</td>
</tr>
<tr>
<td>• Students must select a fruit option at breakfast with their meal, and either a fruit or a vegetable at lunch for the meal to be reimbursable.</td>
</tr>
</tbody>
</table>

Using Food as Reward

It is a prevalent habit to use food as a reward or sometimes withdraw food as punishment. Most parents use this practice occasionally, and some use it almost systematically, starting at a young age. The practice is also commonly used in other settings where children spend time, such as daycare, school, or even athletic settings. Although it might be a good idea to limit some unhealthy but desirable food categories to special occasions, using food as a reward is problematic. Limiting access to some foods and making its access contingent on a particular accomplishment increases the desirability of that type of food. Conversely, encouraging the consumption of some foods renders them less desirable. Therefore, phrases such as “finish your vegetables, and you will get ice cream for dessert” can result in establishing unhealthy eating habits once the child has more autonomy in food choices. Parents should be counseled on such issues and encouraged to choose items other than food as reward, such as inexpensive toys or sporting equipment, family time, special family events, or collectable items. Similar types of behavior are also seen in schools and extra-curricular events. As opposed to rewarding or punishments of food (pizza/candy) daycare providers, teachers, and counselors should be encouraged to use alternative rewards such as minutes of free time, sitting in the teacher’s chair, being the teacher helper, and homework-free nights.

Cultural Considerations in Nutrition and Feeding

Food choices, food preparation, eating patterns, and infant feeding practices all have very deep cultural roots. In fact, beliefs, attitudes, and practices surrounding food and eating are some of the most important components of cultural identity. Therefore, it is not surprising that in multicultural societies, great variability exists in the cultural characteristics of the diet. Even in a world where global marketing forces tend to reduce geographic differences in the types of food, or even brands, that are available, most families, especially during family meals at home, are still much influenced by their cultural background. Therefore, pediatricians should become familiar with the dietary characteristics of various cultures in their community, so that they can identify and address, in a nonjudgmental way and avoiding stereotypes, the potential nutritional issues related to the diet of their patients.

Vegetarianism

Vegetarianism is the practice of following a diet that excludes animal flesh foods, including beef, pork, poultry, fish, and shellfish. There are several variants of the diet, some of which also exclude eggs and/or some products produced from animal labor, such as dairy products and honey. There are many different variations in vegetarianism:
- Veganism: excludes all animal products. It may be part of a larger practice of abstaining from the use of animals products for any purpose.
- Ovo-vegetarianism: includes eggs but not dairy products.
- Lactovegetarianism: includes dairy products but excludes eggs.
- Lacto-ovo-vegetarianism: includes eggs and dairy products.
- Flexitarian: recent term referring to a vegetarian who will occasionally eat meat.

Another expression used for vegetarianism and veganism is “plant-based diets.”

Other dietary practices commonly associated with vegetarianism include fruitarian diet (fruits, nuts, seeds, and other plant matter gathered without harm to the plant); Su vegetarian diet (a diet that excludes all animal products as well as onion, garlic, scallions, leeks, or shallots); a macrobiotic diet (whole grains and beans and, in some cases, fish); and raw vegan diet (fresh and uncooked fruits, nuts, seeds, and vegetables). The safety of these restrictive diets has not been studied in children. These diets can be very limited in macro- and micronutrients and are not recommended for children. Implementing vegetarian diets in teenage girls may be a sign of an eating disorder.

Vegetarianism is considered a healthful and viable diet; both the Academy of Nutrition and Dietetics (formerly the American Dietetic Association) and the Dietitians of Canada have found that a properly planned and well-balanced vegetarian diet can satisfy the nutritional needs of all age groups.
goals for all stages of life. Compared with nonvegetarian diets, vegetari-
ian diets have low levels of saturated fat, cholesterol, and animal
protein, and relatively higher levels of complex carbohydrates, fiber,
magnesium, potassium, folate, vitamins C and E, and phytochemicals.
Vegetarians have a lower body mass index, cholesterol, and blood pres-
sure, and are at decreased risk for cancer and ischemic heart disease.

Specific nutrients of concern in vegetarian diets include:

- **Iron**: Vegetarian diets have similar levels of iron compared to
  nonvegetarian diets, but the iron has lower bioavailability than iron
  from meat sources, and iron absorption may be inhibited by
  other dietary constituents, such as phytate (see Chapter 54). Iron
  stores are lower in vegetarians and vegans than in nonvegetarians;
  and iron deficiency is more common in vegetarian and vegan
  women and children. Foods rich in iron include iron-fortified
  cereals, black beans, cashews, kidney beans, lentils, oatmeal,
  raisins, black-eyed peas, soybeans, sunflower seeds, chickpeas,
  molasses, chocolate, and tempah.

- **Vitamin B<sub>12</sub>**: Plants are not a good source of B<sub>12</sub> (see Chapter
  49.7). Additional vitamin B<sub>12</sub> can be obtained through dairy
  products and eggs; vegans need fortified foods or supplements.
  Breastfeeding by vegan mothers can place an infant at risk for
  vitamin B<sub>12</sub> deficiency.

- **Fatty acids**: Vegetarians and vegans may be at risk for low levels of
  eicosapentaenoic acid (EPA) and DHA. The inclusion of sources of
  linolenic acid (precursor of EPA and DHA), such as walnuts, soy
  products, flaxseed, and canola oils, are recommended.

- **Calcium and vitamin D**: Without supplementation, vegan diets
  are low in calcium and vitamin D putting vegans at risk for
  impaired bone mineralization (see Chapter 51). Vitamin D-OH
  levels should be monitored in vegans and supplemented for levels
  <30 dL. Calcium sources include leafy greens (with low oxalate:
  broccoli, kale, or Chinese cabbage). Calcium and vitamin D are
  found in almond and soy milk, and fortified orange juice.

- **Zinc**: The bioavailability of zinc in plant sources tends to be low
  because of the presence of phytates and fiber that inhibit zinc
  absorption (see Chapter 54). Zinc is found in soy products,
  legumes, grains, cheese, and nuts.

### Organic Foods

Parents may prefer organic foods to feed children secondary to con-
cerns regarding chemical and hormonal treatment of animals and
produce. The nutritional differences between organic and conventional
foods may not be clinically relevant. Children consuming organic
foods have lower or no detectable levels of pesticides in their urine
compared to those consuming nonorganic foods. It remains unclear
whether such a reduction in exposure to chemicals is clinically signifi-
cant. Organic foods tend to have higher antioxidant levels and lower
levels of cadmium. Similarly, despite concerns of parents, the amount
of bovine growth hormone in conventional milk is thought to be
neither significant nor biologically active in humans. Additionally,
milk consumption from estrogen-treated cows does not result in endo-
crine disruptions in infants. However other chemicals in the environ-
ment, such as bisphenol-A (found in plastics), nitrates, endocrine
disruptors, and phthalates, should be avoided. Organic certification of
a food also suggests the food source is not from a genetically modified
nutrient. Because the cost of these foods is generally higher than the
cost of other foods, a prudent approach is to explain to families that
the scientific basis for choosing organic foods is limited, but if it is their
preference and they can afford the added cost, there is no reason not
to eat organic foods.

### Nutrition as Part of Complementary and
Alternative Medicine, Functional Foods,
Dietary Supplements, Vitamin Supplements,
and Botanical and Herbal Products

The use of nutrition or nutritional supplements as complementary or
alternative medicine is increasing, despite limited data on safety and
efficacy, especially in children. Many parents assume that if a food or
supplement is natural or organic, then there is no potential for risk
and some that supplements are beneficial. However, adverse effects of
some dietary supplements have been documented. It is difficult for
pediatricians to compete against the aggressive marketing through
multi-media sources of food supplements to families of healthy and
chronically ill children. Additionally, pediatricians must compete
against the word-of-mouth and advice from people without a scientific
background and those with significant conflicts of interest. One reason
to recommend caution to parents when it comes to dietary supple-
ments, including botanical and herbal products, is that in the United
States, unlike medications, these products are not evaluated for safety
and efficacy before marketing and do not undergo the same level of
quality control as medications. The potential for adverse effects or
simply for inefficacy is therefore high (see Chapter 64).

Pediatricians are often asked by parents if their children need to
receive a daily multivitamin. Unless the child follows a particular diet
that may be poor in one or more nutrients for health, cultural, or
religious reasons, or if the child has a chronic health condition that
puts the child at risk for deficiency in 1 or more nutrients, multivita-
mins are not indicated. A diet that follows the guidelines of MyPlate
contains sufficient nutrients to support healthy growth. Many children
do not follow all the guidelines of MyPlate, and parents and pediatric-
ians may be tempted to use multivitamin supplements just to make
sure that nutrient deficiencies are avoided. Use of a daily multivitamin
supplement can result in a false impression that the child's diet is com-
plete and in decreased efforts to meet dietary recommendations with
food rather than the intake of supplements (see Chapter 44) The
average U.S. diet provides more than a sufficient amount of most nutri-
ents, including most vitamins. Therefore, multivitamins should not be
routinely recommended.

The Institute of Medicine recommends 600 IU of vitamin D per day
in all children who drink less than 1,000 mL/day of vitamin D–fortified
milk, representing the majority of U.S. children and adolescents. In
some specific populations of children at risk for deficiency, supplements
of vitamin B<sub>12</sub>, iron, fat-soluble vitamins, or zinc may be considered.

### Food Safety

Constantly keeping food safety issues in mind is an important aspect
of feeding infants, children, and adolescents. In addition to choking
hazards and food allergies, pediatricians and parents should be aware of
food safety issues related to infectious agents and environmental
contaminants. Food poisoning with bacteria, viruses, or their toxins
are most common with raw or undercooked food, such as oysters, beef,
and eggs, or cooked foods that have not been handled or stored prop-
cerly. The specific bacteria and viruses involved in food poisoning are
described in Chapter 340. Many chemical contaminants, such as heavy
metals, pesticides, and organic compounds, are present in various
foods, usually in small amounts. Because of concerns regarding their
child's neurologic development and cancer risk, many questions arise
from parents, especially after media coverage of isolated incidents. A
recurring debate is the balance between the benefits of seafood for the
growing brain and cardiovascular health and the risk of mercury con-
tamination from consuming large predatory fish species. Pediatricians
need to become familiar with reliable sources of information, such as
the websites of the U.S. Environmental Protection Agency, the FDA,
or the CDC. The Food Safety Modernization Act provides the FDA
with authority to have stricter control over food production and dis-
tribution. The FDA can require that manufacturers develop food safety
plans. A good source of information for patients and parents can be
found at www.foodsafety.gov.

### Nutritional Programming

Emerging epidemiologic evidence suggests that early nutrition starting
during fetal development can have long-term impact on growth, and
adult health. It is well established that undernutrition in early life can
exert a long-term impact in terms of reduced adult height and aca-
demic achievements; other data, however, suggest that intrauterine
growth restriction is associated with obesity and other adult cardiovas-
cular risk factors. Rapid weight gain in infancy, either following intra-
uterine growth restriction or a period of malnutrition, is associated
with an increased risk for later obesity. The process that explains these changes has been termed "programming."

**Preventive Nutrition Counseling in Pediatric Primary Care**
An important part of the primary care well-child visit focuses on nutrition and growth because most families turn to pediatricians for guidance on child nutrition. Preventive nutrition is one of the cornerstones of preventive pediatrics and a critical aspect of anticipatory guidance. The first steps of nutrition counseling are nutritional status assessments, primarily done through growth monitoring and dietary intake assessment. Although dietary assessment is somewhat simple in infants who have a relatively monotonous diet, it is more challenging at older ages. The goals of dietary assessment in the primary care setting need to remain modest and include an idea of the eating patterns (time, location, and environment) and usual diet by asking the parent to describe the child's dietary intake on a typical day or in the last 24 hr. Pediatricians should encourage regularly scheduled meals and 1 or 2 snacks. Alternatively, a basic assessment of the child's consumption of vegetables, fruits, whole grains, low or nonfat dairy products, 100% fruit juice and sugar-sweetened beverages should be assessed. For more ambitious goals of dietary assessment, referral to a registered dietician with pediatric experience is recommended.

Once some understanding of the child's usual diet has been acquired, existing or anticipated nutritional problems should be addressed, such as diet quality, dietary habits, or portion size. For a few nutritional problems, a lack of knowledge can be addressed with nutrition education, but most pediatric preventive nutritional issues, such as overeating or poor food choices, are not the result of lack of parents' knowledge. Therefore, nutrition education alone is insufficient in these situations, and pediatricians need to acquire training in behavior-modification techniques or refer to specialists to assist their patients in engaging in healthy feeding and eating behaviors. The physical, cultural, and family environments in which the child lives should be kept in mind at all times, so that nutrition counseling is relevant and changes are feasible.

One important aspect of nutrition counseling is providing families with sources of additional information and behavioral change tools. Although some handouts are available from government agencies, the AAP, and other professional organizations for families without Internet access, an increasing number of families rely on the Internet to find nutrition information. Therefore, pediatricians need to become familiar with commonly used websites so that they can point families to reliable and unbiased sources of information. Perhaps the most useful websites for reliable and unbiased nutrition information for children are the USDA MyPlate website, the sites of the CDC, FDA, National Institutes of Health, and Institute of Medicine Food and Nutrition Board for government sources and the AAP, American Heart Association, and the Academy of Nutrition and Dietetics (formerly the American Dietetic Association) for professional organization resources. Pediatricians should also be aware of sites that provide biased or even dangerous information, so that they can warn families accordingly. Examples include dieting sites, sites that openly promote dietary supplements or other food products, and the sites of "nonprofit" organizations that are mainly sponsored by food companies or that have other social or political agendas.

**Food Assistance Programs in the USA**
Several programs exist in the United States to ensure sufficient and high-quality nutrition for children of families who cannot always afford optimal nutrition. One of the most popular federal programs is the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC). This program provides nutrition supplements to a large proportion of pregnant women, postpartum women, and children up to their 5th birthday. One of its strengths is that in order to qualify, families need to regularly visit a WIC nutritionist, who can be a useful resource for nutritional counseling. Other popular programs include school lunches, breakfasts, and after-school meals, as well as daycare and summer nutrition programs. Lower-income families are also eligible for the Supplemental Nutrition Assistance Program, formerly known as the Food Stamp Program. This program provides funds directly to families to purchase various food items in regular food stores.

*Bibliography is available at Expert Consult.*
MALNUTRITION AS THE INTERSECTION OF FOOD INSECURITY AND HEALTH INSECURITY

Undernutrition is usually an outcome of 3 factors, often in combination: household food supply, child-caring practices, and access to health and water/sanitation services. In famine and emergency settings, food shortage is the foremost factor, but in many countries with widespread undernutrition, food production or access to food might not be the most limiting factor. More important causes might be repeated childhood infections, especially diarrheal diseases linked with an unsafe environment and lack of exclusive breastfeeding, or inadequate complementary feeding practices, or the lack of time families have available for appropriate infant or maternal care. Figure 46-1 shows some of the many causal factors on the pathway to undernutrition and how they extend from household and community levels to national/international levels. Inequitable distribution of resources because of political, economic, and agricultural policies often denies families their right to adequate land, water, food, healthcare, education, and a safe environment, all of which can influence nutritional status.

Families with few economic resources who know how to care for their children and are enabled to do so can often use available food and health services to produce well-nourished children. If food resources and health services are not available in a community, or not utilized, or not accessible to some families, children might become undernourished. Undernutrition is not confined to low-income countries. It has been noted in chronically ill patients in neonatal and pediatric intensive care units in high-income countries and among patients with burns, HIV, tuberculosis, cystic fibrosis, chronic diarrhea syndromes, malignancies, bone marrow transplantation, and inborn errors of metabolism. Severe malnutrition has been reported in affluent communities in infants whose families believe in fad diets, and in infants with food allergies fed nutritionally inadequate foods such as rice “milk,” which has a very low protein and micronutrient content (Fig. 46-2).

FOOD SECURITY

Food security exists “when all people, at all times, have access to sufficient, safe, nutritious food to maintain a healthy and active life.” Four main dimensions of food security can be identified: availability, access, utilization, and stability. Availability refers to the supply of food (reflecting the level of food production, food stocks, and net trade). Access is at the household level, reflecting purchasing power, household food production, and food/cash transfers received through social safety net programs. The utilization dimension recognizes that even when a household has access to food it is not necessarily shared equitably within a household. Stability refers to being food secure at all times: Examples of situations that affect stability are the “lean seasons” before a harvest, natural disasters, political unrest, and rising food prices. To be food secure, all 4 dimensions must be met simultaneously.
Measuring Food Insecurity

The most commonly used measurement of food insecurity is "under-nourishment" (chronic hunger), and is the proportion of the population who are unable to meet daily energy requirements for light activities. It is an estimate calculated by the Food and Agriculture Organization (FAO) based on country-level Food Balance Sheets. It does not take nutrient adequacy into account, but has the advantage of being available for almost all countries annually (although with a time-lag) and assists in monitoring global trends. In addition, FAO measures food access by asking individuals about their experiences over the last 12 mo, such as whether they ran out of food, or skipped meals. The responses are graded from mild to severe food insecurity.

In 2011-2013, FAO estimated that about 842 million people, or 12% of the world’s population, were undernourished, 98% of whom were in developing countries. The majority are rural poor subsisting on small plots of land or hired as laborers, and urban poor who lack the means to grow or buy food. Alongside the 0.84 billion people who are underfed, there are 1.5 billion who are overfed reflecting global inequalities, and the “double burden of malnutrition” in low- and middle-income countries.

Nutrition, Food Security, and Poverty

Household food security tracks income closely. With rising incomes, very poor households first increase their dietary energy intake to avert hunger. If incomes rise further there is a shift to more expensive staple foods and then to a more varied diet with a greater proportion of energy from animal sources, fruits and vegetables, fats and sugars, and less from cereals, roots and tubers. National economic growth tends to be accompanied by reductions in stunting, but economic growth can pass by the poor if they work in unaffected sectors, or are unable to take advantage of new opportunities because of lack of education, access to credit, or transportation, or if governments do not channel resources accruing from economic growth to healthcare, education, social protection, and other public services and infrastructure. There is good evidence that economic growth reduces poverty, but does not necessarily reduce undernutrition.

Food Security and Nutrition Targets

World leaders collectively agreed to 8 Millennium Development Goals (MDGs) in 2000. MDG 1 aimed to eradicate extreme poverty and hunger. The target to halve the proportion of people whose income is less than $1 per day was reached at the global level 5 yr ahead of the 2015 target. This was greatly helped by the progress made by China and India. Sub-Saharan Africa is unlikely to reach the target. The reductions in hunger are broadly consistent with those of poverty reduction, and rates of undernourishment in developing regions fell from 23.2% in 1990 to 14.3% in 2011-2013. Sub-Saharan Africa is the region least likely to achieve the target of halving undernourishment by 2015. The prevalence of underweight children (another MDG indicator of “hunger”) fell from 29% in 1990 to 17% in 2012 for the
Global Food Security and Nutrition Targets


◆ For meat and dairy foods. Equally challenging actions include limiting climate disruption, increasing the efficiency of food production, reducing waste, and reducing the demand for meat and dairy foods.

Future Food Security

Between now and 2050 the world’s population is expected to rise to around 9 billion, and an increase in food supply of 70-100% will be needed to feed this larger, more urban, and more affluent populace. Over this same period, the world’s food supply is expected to diminish unless action is taken. Accelerating the decline in fertility rates and doubling of smallholder productivity and income, particularly for women, are basic, but difficult, actions to bridge the gap between increasing demand and diminishing supply. Equally challenging actions include limiting climate disruption, increasing the efficiency of food production, reducing waste, and reducing the demand for meat and dairy foods.

Table 46-1 Global Food Security and Nutrition Targets

<table>
<thead>
<tr>
<th>ZERO HUNGER CHALLENGE OBJECTIVES</th>
<th>WORLD HEALTH ASSEMBLY GLOBAL NUTRITION TARGETS FOR 2025</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access to an adequate and stable food supply for all</td>
<td>A 40% reduction in the number of stunted children &lt;5 yr</td>
</tr>
<tr>
<td>Elimination of stunting in children &lt;2 yr and no malnutrition in pregnancy and early childhood</td>
<td>A 50% reduction in anemia in women of reproductive age</td>
</tr>
<tr>
<td>Sustainable food systems</td>
<td>A 30% reduction in low birthweight</td>
</tr>
<tr>
<td>Doubling of smallholder productivity and income, particularly for women</td>
<td>No increase in childhood overweightness</td>
</tr>
<tr>
<td>No loss or waste of food, and responsible consumption</td>
<td>Increase exclusive breastfeeding rates to at least 50% in the first 6 months</td>
</tr>
<tr>
<td>Reduce and maintain childhood wasting to less than 5%</td>
<td>Reduce and maintain childhood wasting to less than 5%</td>
</tr>
</tbody>
</table>


greenhouse gas emissions is essential to minimize climate disruption, hence the aim to (a) cut fossil fuel use by at least half of present levels by 2050 so as to reduce CO₂ emissions and (b) change livestock husbandry and agronomic practices to reduce methane and nitrous oxide emissions.

◆ Increase efficiency of food production: Expanding the area of agricultural land to any large extent (e.g., by deforestation) is not a sustainable option because of adverse consequences on ecosystems and biodiversity, although some expansion of food production could be achieved by switching good quality land away from first-generation biofuels. For example, 40% of the U.S. corn harvest in 2010 went to biofuels. Efforts to increase the intensity of production need to be environmentally sustainable. These include optimizing yields by soil and water conservation, removal of technical and financial constraints faced by farmers, and breeding resource-efficient crops and livestock that are also climate-resilient and pest/disease-resistant.

◆ Reduce waste: Some 30-40% of food is wasted, either between harvesting and the market, or during retail, at home, and in the food service industry. Better transport and storage facilities in developing countries, less stringent sell-by dates, lower cosmetic standards for fruits and vegetables, and ending supersized portions would help reduce waste.

◆ Change diets: As wealth increases, so does the demand for processed foods, meat, dairy products, and fish. About one-third of global cereal production is fed to animals, so reducing consumption of meat from grain-fed livestock and increasing the proportion derived from the most efficient sources (pigs and poultry) would allow more people to be fed from the same amount of land.

UNDERNUTRITION

The greatest risk of undernutrition (underweight, stunting, wasting, and micronutrient deficiencies) occurs in the first 1000 days, from conception to 24 mo of age, and this early damage to growth and development can have adverse consequences in later life on health, intellectual ability, school achievement, work productivity, and earnings. Governments and agencies are therefore advised to focus interventions on this critical window of opportunity. For folate deficiency, which increases the risk of birth defects, this particular window of opportunity is before conception.

Measurement of Undernutrition

The term malnutrition encompasses both ends of the nutrition spectrum, from undernutrition to overweight. Many poor nutritional outcomes begin in utero and are manifest as low birthweight (LBW, <2,500 g). Preterm delivery and fetal growth restriction are the 2 main

...
Table 46-2 Classification of Undernutrition

<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
<th>INDEX</th>
<th>GRADING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gomez (underweight)</td>
<td>90-75% of median weight-for-age 75-60% &lt;60%</td>
<td>Grade 1 (mild) Grade 2 (moderate) Grade 3 (severe)</td>
</tr>
<tr>
<td>Waterlow (wasting)</td>
<td>90-80% of median weight-for-height &lt;70%</td>
<td>Mild Severe</td>
</tr>
<tr>
<td>Waterlow (stunting)</td>
<td>95-90% of median height-for-age 90-85% &lt;85%</td>
<td>Mild Severe</td>
</tr>
<tr>
<td>WHO (wasting)</td>
<td>&lt;−2 to &gt;−3 SD weight-for-height &lt;=3</td>
<td>Moderate Severe</td>
</tr>
<tr>
<td>WHO (stunting)</td>
<td>&lt;−2 to &gt;−3 SD height-for-age &lt;=3</td>
<td>Moderate Severe</td>
</tr>
<tr>
<td>WHO (wasting) (for age group 6-59 mo)</td>
<td>115-125 mm mid-upper arm circumference &lt;115 mm</td>
<td>Moderate Severe</td>
</tr>
</tbody>
</table>

Figure 46-3 Measuring mid-upper arm circumference. (Image courtesy of Nyani Quarmyne/Panos Pictures.)

colored fruits and vegetables and dark green leaves) (see Chapter 48). The prevalence of clinical deficiency is assessed from symptoms and signs of xerophthalmia (principally night blindness and Bitot spots). Subclinical deficiency is defined as serum retinol concentration <0.70 μmol/L. Vitamin A deficiency is the leading cause of preventable blindness in children. It is also associated with a higher morbidity and mortality among young children.

Iodine deficiency is the main cause of preventable mental impairment (see Chapter 54). An enlarged thyroid (goiter) is a sign of deficiency. Severe deficiency in pregnancy causes fetal loss and permanent damage to the brain and central nervous system in surviving offspring (cretinism). It can be prevented by iodine supplementation before conception or during the first trimester of pregnancy. Postnatal iodine deficiency is associated with impaired mental function and growth retardation. The median urinary iodine concentration in children ages 6-12 yr is used to assess the prevalence of deficiency in the general population, and a median of <100 μg/L indicates insufficient iodine intake.

Iron-deficiency anemia is common in childhood either from low iron intakes or poor absorption, or as a result of illness or parasite infection (see Chapter 54). Women also have relatively high rates of anemia as a result of menstrual blood loss, pregnancy, low iron intakes, poor absorption, and illness. Hemoglobin cutoffs to define anemia are 110 g/L for children 6-59 mo, 115 g/L for children 5-11 yr, and 120 g/L for children 12-14 yr. Cutoffs to define anemia for nonpregnant women are 120 g/L, 110 g/L for pregnant women, and 130 g/L for men.

Zinc deficiency increases the risk of morbidity and mortality from diarrhea, pneumonia, and possibly other infectious diseases (see Chapter 54). Zinc deficiency also has an adverse effect on linear growth. Deficiency at the population level is assessed from dietary zinc intakes.

Prevalence of Undernutrition

It is estimated that approximately 15% of births in low- and middle-income countries in 2010 were LBW. Rates of LBW are highest (26%) in southern Asia, and are twice those of sub-Saharan Africa. India accounts for approximately 40% of the world’s low-weight births. Globally, in 2011 16% of children <5 yr of age were underweight (weight-for-age <−2 SD). The global prevalence of stunting (height-for-age <−2 SD) has declined from an estimated 40% to 26% over the last 20 yr, with the greatest reductions having taken place in Asia. Stunting prevalence is now highest in the African region (36% prevalence). Wasting (weight-for-height <−2 SD) affects 8% of children <5 yr, the prevalence having changed little over the past 2 decades. These figures represent 101 million underweight children, 165 million stunted children, and 52 million wasted children.

Asia carries 69% of the global burden of underweight children, 58% of the global burden of stunted children, and 70% of the global burden
of wasted children because of the combination of large population size and high prevalence. Africa carries most of the remaining global burden. For children <5 yr, the global prevalence is estimated to be 33% for vitamin A deficiency, 29% for iodine deficiency, 17% for zinc deficiency, and 18% for iron-deficiency anemia. Prevalence of micronutrient deficiencies tends to be highest in Africa. For pregnant women, the estimated prevalence of vitamin A deficiency is 15% and for iron-deficiency anemia 19%.

Rates of clinical deficiency of vitamin A in children <5 yr have been declining, probably as a result of high-dose vitamin A supplementation programs and measles vaccination (as measles leads to sizeable urinary loss of vitamin A), but subclinical deficiency remains widespread (more than 90 million children). Large-scale availability of iodized salt has reduced rates of iodine deficiency substantially, and iodized salt now reaches an estimated 70% of households. In contrast, progress in reducing rates of iron-deficiency anemia is slow, and rates remain largely static.

**Consequences of Undernutrition**

The most profound consequence of undernutrition is premature death (Table 46-3). Fetal growth restriction together with suboptimal breastfeeding in the first month of life contribute to 19% of all deaths in children <5 yr (1.3 million deaths/yr). When the effects of stunting, wasting and deficiencies of vitamin A and zinc are also considered, these 6 items jointly contribute to 45% of global child deaths (3.1 million deaths/yr), and many more are disabled or stunted for life. Anemia contributes to over one-quarter of maternal deaths.

The risk of child death from infectious diseases increases even with mild undernutrition, and as the severity of undernutrition increases, the risk increases exponentially (Table 46-4). Undernutrition impairs immune function and other host defenses, consequently childhood infections are more severe and longer lasting in undernourished children and more likely to be fatal compared with the same illnesses in well-nourished children. Also, infections can adversely affect nutritional status, and young children can quickly enter a cycle of repeated infections and ever-worsening malnutrition. Even for the survivors, physical and cognitive damage as a result of undernutrition can impact their future health and economic well-being. For girls, the cycle of undernutrition is passed on to the next generation when undernourished women give birth to LBW babies.

Fetal growth restriction and early childhood undernutrition also have consequences for adult chronic illness. LBW is associated with an increased risk of hypertension, stroke, and type 2 diabetes in adults. The increased risk is thought to reflect “fetal programming,” a process by which fetal undernutrition leads to permanent changes in the structure and metabolism of organs and systems that manifest as disease in later life. The risk is exacerbated by low weight gain during the first 2 yr of life. The increased risk of adult chronic disease emanating from undernutrition in early life is a particular challenge to low-income countries with rapid economic growth.

Stunting before the age of 3 yr is associated with poorer motor and cognitive development and altered behavior in later years. The effect is

### Table 46-3

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>ATTRIBUTABLE DEATHS</th>
<th>% OF TOTAL DEATHS &lt;5 YR</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Fetal growth restriction (&lt;1 mo)</td>
<td>817,000</td>
<td>11.8</td>
</tr>
<tr>
<td>(b) Stunting (1-59 mo)</td>
<td>1,017,000</td>
<td>14.7</td>
</tr>
<tr>
<td>(c) Wasting (1-59 mo)</td>
<td>875,000</td>
<td>12.6</td>
</tr>
<tr>
<td>(d) Zinc deficiency (12-59 mo)</td>
<td>116,000</td>
<td>1.7</td>
</tr>
<tr>
<td>(e) Vitamin A deficiency (6-59 mo)</td>
<td>157,000</td>
<td>2.3</td>
</tr>
<tr>
<td>(f) Suboptimal breastfeeding (0-23 mo)</td>
<td>804,000</td>
<td>11.6</td>
</tr>
<tr>
<td>Joint effects of (a) + (f)</td>
<td>1,348,000</td>
<td>19.4</td>
</tr>
<tr>
<td>Joint effects of all 6 factors</td>
<td>3,097,000</td>
<td>44.7</td>
</tr>
</tbody>
</table>

6-13 DQ (developmental quotient) points. Iodine and iron deficiencies also lead to loss of cognitive potential. Indications are that children living in areas of chronic iodine deficiency have an average reduction in IQ of 12-13.5 points compared with children in iodine-sufficient areas. Iron deficiency has a detrimental effect on the motor development of children <4 yr and on cognition of school-age children. The estimated deficit is 1.73 IQ points for each 10 g/L decrease in hemoglobin concentration.

Undernutrition can have substantial economic consequences for survivors and their families. The consequences can be quantified in 5 categories: increased costs of healthcare, either neonatal care for LBW babies or treatment of illness for infants and young children; productivity losses (and hence reduced earnings) associated with smaller stature and muscle mass; productivity losses from reduced cognitive ability and poorer school performance; increased costs of chronic diseases associated with fetal and early child malnutrition; and consequences of maternal undernutrition on future generations. The impact of nutrition on earnings appears to be independent of the effects of childhood deprivation.

### Key Interventions

Interventions to address child undernutrition can be divided into those that address immediate causes (nutrition-specific interventions) and those that address underlying causes (nutrition-sensitive interventions) (Table 46-5). In the short-term, nutrition-specific interventions (e.g., salt iodization) can have substantial impacts even in the absence of economic growth, and micronutrient interventions (supplementation and fortification) are consistently ranked by economists of the Copenhagen Consensus Center as the most cost-effective investment. Increased attention is being given to nutrition-sensitive interventions as the best means of sustainably eliminating malnutrition, and to multisectoral policies that harness the synergism between the 2 types of intervention. Cross-sectoral linkages between agriculture, nutrition, and health are 1 example.

To reduce the adverse consequences of undernutrition on mortality, morbidity, and cognitive development, interventions must encompass both fetal and postnatal periods. Preventing LBW is essential, with emphasis on prevention of low maternal BMI and anemia, and in the longer term, prevention of low maternal stature. Other measures include smoking cessation, birth spacing, delaying pregnancy until after 18 yr of age, and intermittent preventive treatment of malaria. In the postnatal period, promotion and support of exclusive breastfeeding is a high priority. Although the Baby Friendly Hospital Initiative has a marked benefit on rates of exclusive breastfeeding in hospital, postnatal counseling from community workers or volunteers is needed to facilitate continuation of exclusive breastfeeding at home for 6 mo. Most studies show a lower risk of HIV transmission with exclusive breastfeeding than with mixed breastfeeding. The risk of transmission of HIV by breastfeeding is approximately 5-20% depending on duration, but can be reduced to <2% with antiretroviral drugs. Even without antiretroviral drugs, exclusively breastfed children of HIV-infected mothers in low-income countries have lower mortality than non-breastfed children, as the latter are at increased risk of death from diarrhea and pneumonia.

Interventions to improve infant feeding must be designed for the local setting and thus require careful formative research during their development. Messages should be few in number, feasible, and culturally appropriate. For complementary feeding, nutrient-rich, energy-dense mixtures of foods, and responsive feeding, are often emphasized. Where adequate complementary feeding is difficult to achieve and subclinical deficiencies are common, high-dose vitamin A supplementation every 6 mo in children <5 yr of age can reduce child mortality by 5-15% and zinc supplementation can reduce 1-4 yr mortality by 18%, diarrhea incidence by 13%, and pneumonia incidence by 19%. Monitoring of child growth provides an early alert to a nutrition or health problem but is only worthwhile if accompanied by good counseling and growth promotion activities. The impact of growth monitoring and promotion will be related to coverage, intensity of contact, health worker performance and communications skills, adequacy of resources, and the motivation and ability of families to follow agreed actions.

### Clinical Manifestations and Treatment of Undernutrition

Treatment of vitamin and mineral deficiencies is discussed in Chapters 48-54. Treatment of low birthweight and intrauterine growth restriction are discussed respectively in Chapter 97.

### SEVERE ACUTE MALNUTRITION

Severe acute malnutrition is defined as severe wasting and/or bilateral edema.

Severe wasting is extreme thinness diagnosed by a weight-for-height (or weight) below −3 SD of the WHO Child Growth Standards. In children ages 6-59 mo, a mid-upper arm circumference <115 mm also denotes extreme thinness: a color-banded tape (see Fig. 46-3) is a convenient way of screening children in need of treatment.

**Bilateral edema** is diagnosed by grasping both feet, placing a thumb on top of each, and pressing gently but firmly for 10 seconds. A pit (dent) remaining under each thumb indicates bilateral edema.

This definition of severe acute malnutrition distinguishes wasted/edematous children from those who are stunted, as the latter (although underweight) are not a priority for acute clinical care as their deficits in height and weight cannot be corrected in the short term. The previous name *protein-energy malnutrition* is avoided, as it oversimplifies the complex multifactorial etiology. Other terms are *marasmus* (severe wasting), *kwashiorkor* (characterized by edema), and *marasmic-kwashiorkor* (severe wasting + edema).

Children with severe acute malnutrition have had a diet insufficient in energy and nutrients relative to their needs. The magnitude of the deficits will differ depending on the duration of inadequacy, quantity and diversity of food consumed, presence of antinutrients (such as phytate), individual variation in requirements, and number and severity of coexisting infections and their duration. Infections can lead to profound nutrient deficits and imbalances: For example, amino acids are diverted to form acute-phase proteins and there are losses through diarrhea of potassium, magnesium, vitamin A, and zinc, and of glycine and taurine linked to small bowel bacterial overgrowth. Deficits can

### Table 46-5 Examples of Nutrition-Specific and Nutrition-Sensitive Interventions

<table>
<thead>
<tr>
<th>NUTRITION-SPECIFIC INTERVENTIONS</th>
<th>NUTRITION-SENSITIVE INTERVENTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promotion and support for exclusive breastfeeding for 6 mo, and continued breastfeeding for at least 2 yr</td>
<td>Increased access to affordable, nutritious food; smallholder agriculture; credit and microfinance</td>
</tr>
<tr>
<td>Promotion of adequate, timely, and safe complementary feeding from 6 mo</td>
<td>Postharvest food processing and preservation</td>
</tr>
<tr>
<td>Increased micronutrient intake through dietary diversity</td>
<td>Vaccination against neonatal and childhood illness; access to healthcare</td>
</tr>
<tr>
<td>Micronutrient supplements for pregnant women (iron/folate) and young children (vitamin A, iron, zinc) in deficient areas</td>
<td>Improved water/sanitation and hygiene (e.g., handwashing with soap)</td>
</tr>
<tr>
<td>Zinc supplements to children during and after diarrhea (10-20 mg/day for 2 wk)</td>
<td>Education; women’s empowerment; gender equality</td>
</tr>
<tr>
<td>Prevention and treatment of severe acute malnutrition</td>
<td>Social protection (e.g., cash transfers)</td>
</tr>
<tr>
<td>Crop biofortification, food fortification, salt iodization</td>
<td>Malaria prevention (vector control/bednets); intermittent preventive treatment during pregnancy and in children 3-59 mo</td>
</tr>
<tr>
<td>Reduced heavy physical activity in pregnancy</td>
<td>Birth spacing; delaying pregnancy until after 18 yr of age</td>
</tr>
</tbody>
</table>
also arise from increased nutrient utilization in response to noxae (e.g.,
cysteine and methionine to detoxify dietary cyanogens). Heterogeneity in
the extent and nature of the deficits and imbalances, reflecting the
diverse pathways to severe acute malnutrition, helps explain why
affected children differ in their clinical presentation and degree of
metabolic disturbance. Children who develop edematous malnutrition
are more likely than nonedematous children to have been exposed to
noxae that generate oxidative stress and/or to have greater deficits in
free radical-scavenging antioxidants (glutathione, vitamins A, C, and
E, and essential fatty acids) or cofactors (zinc, copper, selenium).

Clinical Manifestations of Severe Acute Malnutrition (Table 46-6)

Severe wasting (Fig. 46-4) is most visible on the thighs, buttocks, and
upper arms, and over the ribs and scapulae where loss of fat and skele-
tal muscle is greatest. Wasting is preceded by failure to gain weight
and then by weight loss. The skin loses turgor and becomes loose as
subcutaneous tissues are broken down to provide energy. The face may
retain a relatively normal appearance, but eventually becomes wasted
and wizened. The eyes may be sunken from loss of retroorbital fat, and
lachrymal and salivary glands may atrophy leading to lack of tears and
a dry mouth. Weakened abdominal muscles and gas from bacterial
overgrowth of the upper gut may lead to a distended abdomen. Severely
wasted children are often fretful and irritable.

In edematous malnutrition, the edema is most likely to appear first
in the feet and then in the lower legs. It can quickly develop into gen-
eralized edema affecting also the hands, arms, and face (Fig. 46-5). Skin
changes commonly occur over the swollen limbs and include dark,
cracked peeling patches (flaky paint dermatosis) with pale skin
underneath that is easily infected. The hair is sparse and easily pulled
out and may lose its curl. In dark-haired children, the hair may turn
pale or reddish. The liver is often enlarged with fat. Children with edema
are miserable and apathetic, and often refuse to eat.

Pathophysiology

When a child’s intake is insufficient to meet daily needs, physiologic
and metabolic changes take place in an orderly progression to conserve
energy and prolong life. This process is called reductive adaptation. Fat
stores are mobilized to provide energy. Later protein in muscle, skin,
and the gastrointestinal tract is mobilized. Energy is conserved by
reducing physical activity and growth, reducing basal metabolism and
the functional reserve of organs and by reducing inflammatory and
immune responses. These changes have important consequences:
¬ The liver makes glucose less readily, making the child more prone
to hypoglycemia. It produces less albumin, transferrin, and other
transport proteins. It is less able to cope with excess dietary
protein and to excrete toxins.
¬ Heat production is less, making the child more vulnerable to
hypothermia.
¬ The kidneys are less able to excrete excess fluid and sodium,
and fluid easily accumulates in the circulation, increasing the risk of
fluid overload.
¬ The heart is smaller and weaker and has a reduced output, and
fluid overload readily leads to death from cardiac failure.
¬ Sodium builds up inside cells due to leaky cell membranes and
reduced activity of the sodium/potassium pump, leading to excess
body sodium, fluid retention, and edema.
¬ Potassium leaks out of cells and is excreted in urine, contributing
to electrolyte imbalance, fluid retention, edema, and anorexia.
¬ Loss of muscle protein is accompanied by loss of potassium,
magnesium, zinc, and copper.

<table>
<thead>
<tr>
<th>Table 46-6</th>
<th>Clinical Signs of Malnutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>SITE</td>
<td>SIGNS</td>
</tr>
<tr>
<td>Face</td>
<td>Moon face (kwashiorkor), simian facies (marasmus)</td>
</tr>
<tr>
<td>Eye</td>
<td>Dry eyes, pale conjunctiva, Bitot spots (vitamin A), periocular edema</td>
</tr>
<tr>
<td>Mouth</td>
<td>Angular stomatitis, cheilitis, glossitis, spongy bleeding gums (vitamin C), parotid enlargement</td>
</tr>
<tr>
<td>Teeth</td>
<td>Enamel mottling, delayed eruption</td>
</tr>
<tr>
<td>Hair</td>
<td>Dull, sparse, brittle hair, hypopigmentation, flag sign (alternating bands of light and normal color), broomstick eyelashes, alopecia</td>
</tr>
<tr>
<td>Skin</td>
<td>Loose and wrinkled (marasmus), shiny and edematous (kwashiorkor), dry, follicular hyperkeratosis, patchy hyper- and hypopigmentation (crazy paving or flaky paint dermatoses), erosions, poor wound healing</td>
</tr>
<tr>
<td>Nails</td>
<td>Koilonychia, thin and soft nail plates, fissures, or ridges</td>
</tr>
<tr>
<td>Musculature</td>
<td>Muscle wasting, particularly buttocks and thighs; Chvostek or Trousseau sign (hypocalcemia)</td>
</tr>
<tr>
<td>Skeletal</td>
<td>Deformities, usually as a result of calcium, vitamin D, or vitamin C deficiencies</td>
</tr>
<tr>
<td>Abdomen</td>
<td>Distended: hepatomegaly with fatty liver; ascites may be present</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Bradycardia, hypotension, reduced cardiac output, small vessel vasculopathy</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Global developmental delay, loss of knee and ankle reflexes, impaired memory</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Pallor, petechiae, bleeding diathesis</td>
</tr>
<tr>
<td>Behavior</td>
<td>Lethargic, apathetic, irritable on handling</td>
</tr>
</tbody>
</table>


Figure 46-4 Child with severe wasting.
● The gut produces less gastric acid and enzymes. Motility is reduced, and bacteria may colonize the stomach and small intestine, damaging the mucosa and deconjugating bile salts. Digestion and absorption are impaired.
● Cell replication and repair are reduced, increasing the risk of bacterial translocation through the gut mucosa.
● Immune function is impaired, especially cell-mediated immunity. The usual responses to infection may be absent, even in severe illness, increasing the risk of undiagnosed infection.

● Red cell mass is reduced, releasing iron which requires glucose and amino acids to be converted to ferritin, increasing the risk of hypoglycemia and amino acid imbalances. If conversion to ferritin is incomplete, unbound iron promotes pathogen growth and formation of free radicals.
● Micronutrient deficiencies limit the body’s ability to deactivate free radicals, which cause cell damage. Edema and hair/skin changes are outward signs of cell damage.

When prescribing treatment it is essential to take these changes in function into account, otherwise organs and systems will be overwhelmed and death will rapidly ensue.

**Principles of Treatment**

Figure 46-6 shows the 10 steps of treatment, which are separated into 2 phases referred to as stabilization and rehabilitation. These steps apply to all clinical forms and all geographic locations, including North America and Europe. The aim of the stabilization phase is to repair cellular function, correct fluid and electrolyte imbalance, restore homeostasis, and prevent death from the interlinked triad of hypoglycemia, hypothermia, and infection. The aim of the rehabilitation phase is to restore wasted tissues (i.e., catch-up growth). It is essential that treatment proceeds in an ordered progression and that the metabolic machinery is repaired before any attempt is made to promote weight gain. Pushing ahead too quickly risks inducing the potentially fatal “refeeding syndrome.”

Caregivers bring children to health facilities because of illness, rarely because of their malnutrition. A common mistake among healthcare providers is to focus on the illness and treat as for a well-nourished child. This approach ignores the deranged metabolism in malnourished children and can be fatal. Such children should be considered as severely malnourished with a complication, and treatment should follow the 10 steps. Two other potentially fatal mistakes are to treat edema with a diuretic and to give a high-protein diet in the early phase of treatment.

**Emergency treatment:** Table 46-7 summarizes the therapeutic directives for malnourished children with shock and other emergency conditions. Note that treatment of shock in these children is different (less rapid, smaller volume, different fluid) from treatment of shock in well-nourished children. This difference is because shock from dehydration and sepsis often coexist and are difficult to differentiate on clinical grounds. Thus one has to be guided by the response to treatment: children with dehydration respond to IV fluid whereas those with septic shock will not respond. Since severely malnourished children can quickly succumb to fluid overload, they must be monitored closely.

**Stabilization:** Table 46-8 summarizes the therapeutic directives for stabilization steps 1-7. Giving broad-spectrum antibiotics (Table 46-9) and feeding frequent small amounts of F75 (a specially formulated low-lactose milk with 75 kcal and 0.9 g protein per

---

**Figure 46-5** Child with generalized edema.

**Figure 46-6** The 10 steps of treatment for severe acute malnutrition and their approximate time frames.
Therapeutic Directives for Stabilization

Replace stool losses

Emergency Treatment in Severe Malnutrition

### Table 46-7  Emergency Treatment in Severe Malnutrition

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>IMMEDIATE ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shock</td>
<td></td>
</tr>
</tbody>
</table>
| • Lethargic or unconscious and cold hands | 1. Give oxygen  
| • Slow capillary refill (longer than 3 sec) | 2. Give sterile 10% glucose (5 mL/kg) by IV  
| • Weak fast pulse | 3. Give IV fluid at 15 mL/kg over 1 hr, using:  
|                  | • Ringer’s lactate with 5% dextrose or  
|                  | • Half-normal saline with 5% dextrose or  
|                  | • Half-strength Darrow solution with 5% dextrose  
|                  | • If all of the above are unavailable, Ringer lactate  
|                  | 4. Measure and record pulse and respirations at the start and every 10 minutes  
|                  | If there are signs of improvement (pulse and respiratory rates fall) repeat IV 15 mL/kg for 1 more hr. Then switch to oral or nasogastric rehydration with ReSoMal, 5-10 mL/kg in alternate hr (see Table 46-8 step 3)  
|                  | If there are no signs of improvement assume septic shock and:  
|                  | 1. Give maintenance fluid IV (4 mL/kg/hr) while waiting for blood  
|                  | 2. Order 10 mL/kg fresh whole blood and transfuse slowly over 3 hr. If signs of heart failure, give 5-7 mL/kg packed cells rather than whole blood  
|                  | 3. Give furosemide 1 mL/kg IV at the start of the transfusion  
|                  | 1. Give furosemide 1 mL/kg IV at the start of the transfusion  
|                  | 1. Give ReSoMal after each watery stool  
|                  | 2. Give ReSoMal (37.5 mmol Na/L) is a low-sodium rehydration solution for malnutrition  
|                  | 3. Monitor hourly and stop if signs of overload develop (pulse rate increases by 25 beats/min and respiratory rate by 5 breaths/min; increasing edema; engorged jugular veins)  
|                  | 4. Stop when rehydrated (3 or more signs of hydration: less thirsty, passing urine, skin pinch less slow, eyes less sunken, moist mouth, tears, less lethargic, improved pulse and respiratory rate). |

<table>
<thead>
<tr>
<th>Condition</th>
<th>IMMEDIATE ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td>Blood glucose less than 3 mmol/L</td>
</tr>
<tr>
<td>Severe dehydration</td>
<td>Do not give IV fluids except in shock</td>
</tr>
</tbody>
</table>
| Very severe anemia | Hb less than 4 g/dL | If very severe anemia (or Hb 4-6 g/dL AND respiratory distress):  
|                  | 1. Give whole blood 10 mL/kg slowly over 3 hr. If signs of heart failure, give 5-7 mL/kg packed cells rather than whole blood  
|                  | 2. Give furosemide 1 mL/kg IV at the start of the transfusion  
| Emergency eye care | Corneal ulceration | If corneal ulceration:  
|                  | 1. Give vitamin A immediately (age <6 mo 50,000 IU, 6-12 mo 100,000 IU, >12 mo 200,000 IU)  
|                  | 2. Instill 1 drop atropine (1%) into affected eye to relax the eye and prevent the lens from pushing out |

### Table 46-8  Therapeutic Directives for Stabilization

<table>
<thead>
<tr>
<th>STEP</th>
<th>PREVENTION</th>
<th>TREATMENT</th>
</tr>
</thead>
</table>
| 1. Prevent/treat hypoglycemia blood glucose <3 mmol/L | Avoid long gaps without food and minimize need for glucose  
| 1. Feed immediately  
| 2. Feed every 3 hr day and night (2 hr if ill)  
| 3. Feed on time  
| 4. Keep warm  
| 5. Treat infections (they compete for glucose)  
| Note: Hypoglycemia and hypothermia often coexist, and are signs of severe infection | If conscious:  
| 1. 10% glucose (50 mL), or a feed (see step 7), or 1 teaspoon sugar under the tongue-whichever is quickest  
| 2. Feed every 2 hr for at least the first day. Initially give ⅓ of feed every 30 min  
| 3. Keep warm  
| 4. Start broad-spectrum antibiotics | If unconscious:  
| 1. Immediately give sterile 10% glucose (5 mL/kg) by IV  
| 2. Feed every 2 hr for at least first day. Initially give ⅓ of feed every 30 min. Use nasogastric (NG) tube if unable to drink  
| 3. Keep warm  
| 4. Start broad-spectrum antibiotics |
| 2. Prevent/treat hypothermia axillary <35°C (95°F); rectal <35.5°C (95.9°F) | Keep warm and dry and feed frequently  
| 1. Avoid exposure  
| 2. Dress warmly, including head and cover with blanket  
| 3. Keep room hot; avoid draughts  
| 4. Change wet clothes and bedding  
| 5. Do not bathe if very ill  
| 6. Feed frequently day and night  
| 7. Treat infections | Actively rewarm  
| 1. Feed  
| 2. Skin-to-skin contact with carer (“kangaroo technique”) or dress in warmed clothes, cover head, wrap in warmed blanket and provide indirect heat (e.g. heater; transwarmer mattress; incandescent lamp)  
| 3. Monitor temperature hourly (or every 30 min if using heater)  
| 4. Stop rewarming when rectal temperature is 36.5°C (97.7°F) |
| 3. Prevent/treat dehydration | Replace stool losses  
| 1. Give ReSoMal after each watery stool  
| 2. Then give 5-10 mL/kg in alternate hours for up to 10 hr. Amount depends on stool loss and eagerness to drink. Feed in the other alternate hour  
| 3. Monitor hourly and stop if signs of overload develop (pulse rate increases by 25 beats/min and respiratory rate by 5 breaths/min; increasing edema; engorged jugular veins)  
| 4. Stop when rehydrated (3 or more signs of hydration: less thirsty, passing urine, skin pinch less slow, eyes less sunken, moist mouth, tears, less lethargic, improved pulse and respiratory rate). | Do not give IV fluids unless the child is in shock  
| 1. Give ReSoMal 5 mL/kg every 30 min for first 2 hr orally or NG tube  
| 2. Then give 5-10 mL/kg in alternate hours for up to 10 hr. Amount depends on stool loss and eagerness to drink. Feed in the other alternate hour  
| 3. Monitor hourly and stop if signs of overload develop (pulse rate increases by 25 beats/min and respiratory rate by 5 breaths/min; increasing edema; engorged jugular veins)  
| 4. Stop when rehydrated (3 or more signs of hydration: less thirsty, passing urine, skin pinch less slow, eyes less sunken, moist mouth, tears, less lethargic, improved pulse and respiratory rate). |
**Table 46-8** Therapeutic Directives for Stabilization—cont’d

<table>
<thead>
<tr>
<th>STEP</th>
<th>PREVENTION</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Correct electrolyte imbalance—deficit of potassium and magnesium, excess sodium</td>
<td>Minimize risk of cross-infection 1. Avoid overcrowding 2. Wash hands 3. Give measles vaccine to immunized children age ≥6 mo</td>
<td>Give extra potassium (4 mmol/kg/day) and magnesium (0.6 mmol/kg/day) for at least 2 wk (see Table 46-12) Note: Potassium and magnesium are already added in Nutriset F75 and F100 packets</td>
</tr>
<tr>
<td>5. Prevent/treat infections</td>
<td>Infections are often silent. Starting on the first day, give broad-spectrum antibiotics to all children. 1. For antibiotic choices/schedule see Table 46-9 2. Ensure all doses are given, and given on time 3. Cover skin lesions so they do not become infected Note: Avoid steroids as they depress immune function</td>
<td></td>
</tr>
</tbody>
</table>

**Table 46-9** Recommended Antibiotics*

<table>
<thead>
<tr>
<th>If no complications</th>
<th>Amoxicillin oral 25 mg/kg twice daily for 5 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>If complications (shock, hypoglycemia, hypothermia, skin lesions, respiratory or urinary tract infections, or lethargy/sickly)</td>
<td>Gentamicin (7.5 mg/kg IV or IM) once daily for 7 days and Ampicillin (50 mg/kg IV or IM) every 6 hr for 2 days, then oral amoxicillin (25-40 mg/kg) every 8 hr for 5 days</td>
</tr>
</tbody>
</table>

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100 mL to which potassium, magnesium, and micronutrients are added), will reestablish metabolic control, treat edema, and restore appetite. The parenteral route should be avoided; children who lack appetite should be fed by nasogastric tube, as nutrients delivered within the gut lumen help in its repair. Table 46-10 gives recipes for preparing the special feeds, and their nutrient composition. Two recipes for F75 are shown: one requires no cooking, the other is cereal-based and has a lower osmolality, which may benefit children with persistent diarrhea. F75 is also available commercially in which maltodextrins replace some of the sugar and to which potassium, magnesium, minerals, and vitamins are already added.

Dehydration status is easily misdiagnosed in severely wasted children, as the usual signs (such as slow skin pinch, sunken eyes) may be present even without dehydration. Rehydration must therefore be closely monitored for signs of fluid overload. Serum electrolyte levels can be misleading because of sodium leaking from the blood into cells and potassium leaking out of cells. Keeping the intake of electrolytes and nutrients constant (see Table 46-10) allows systems to stabilize more quickly than adjusting intake in response to laboratory results.

Table 46-11 gives a recipe for the special rehydration solution used in severe malnutrition (ReSoMal). Therapeutic Combined Mineral Vitamin mix (CMV) contains electrolytes, minerals, and vitamins and is added to ReSoMal and feeds. If unavailable, potassium, magnesium, zinc, and copper can be added as an electrolyte/mineral stock solution (Table 46-12 provides a recipe) and a multivitamin supplement given separately.

**Rehabilitation**: The signals for entry to this phase are reduced/minimal edema and return of appetite. A controlled transition over 3 days is recommended to prevent the “refeeding syndrome.” After the transition,
Table 46-10  Recipes for Milk Formulas F75 and F100

<table>
<thead>
<tr>
<th></th>
<th>F75&lt;sup&gt;b&lt;/sup&gt;</th>
<th>F75&lt;sup&gt;c&lt;/sup&gt;</th>
<th>F100&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dried skimmed milk (g)</strong></td>
<td>25</td>
<td>25</td>
<td>80</td>
</tr>
<tr>
<td><strong>Sugar (g)</strong></td>
<td>100</td>
<td>70</td>
<td>50</td>
</tr>
<tr>
<td><strong>Cereal flour (g)</strong></td>
<td>—</td>
<td>35</td>
<td>—</td>
</tr>
<tr>
<td><strong>Vegetable oil (g)</strong></td>
<td>30</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td><strong>Electrolyte/mineral solution (mL)</strong></td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td><strong>Water: make up to (mL)</strong></td>
<td>1000</td>
<td>1000</td>
<td>1000</td>
</tr>
</tbody>
</table>

**Content/100 mL**

<table>
<thead>
<tr>
<th></th>
<th>F75&lt;sup&gt;b&lt;/sup&gt;</th>
<th>F75&lt;sup&gt;c&lt;/sup&gt;</th>
<th>F100&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Energy (kcal)</strong></td>
<td>75</td>
<td>75</td>
<td>100</td>
</tr>
<tr>
<td><strong>Protein (g)</strong></td>
<td>0.9</td>
<td>1.1</td>
<td>2.9</td>
</tr>
<tr>
<td><strong>Lactose (g)</strong></td>
<td>1.3</td>
<td>1.3</td>
<td>4.2</td>
</tr>
<tr>
<td><strong>Potassium (mmol)</strong></td>
<td>4.0</td>
<td>4.2</td>
<td>6.3</td>
</tr>
<tr>
<td><strong>Sodium (mmol)</strong></td>
<td>0.6</td>
<td>0.6</td>
<td>1.9</td>
</tr>
<tr>
<td><strong>Magnesium (mmol)</strong></td>
<td>0.43</td>
<td>0.46</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>Zinc (mg)</strong></td>
<td>2.0</td>
<td>2.0</td>
<td>2.3</td>
</tr>
<tr>
<td><strong>Copper (mg)</strong></td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>% Energy from protein</strong></td>
<td>5</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td><strong>% Energy from fat</strong></td>
<td>32</td>
<td>32</td>
<td>53</td>
</tr>
<tr>
<td><strong>Osmolality (mOsm/L)</strong></td>
<td>413</td>
<td>334</td>
<td>419</td>
</tr>
</tbody>
</table>

Whisk at high speed to prevent oil from separating out.

<sup>a</sup>See Table 46-12 for recipe, or use commercially available therapeutic Combined Mineral Vitamin mix (CMV).

<sup>b</sup>A comparable F75 can be made from 35 g dried whole milk, 100 g sugar, 20 g oil, 20 mL electrolyte/mineral solution, and water to 1000 mL; or from 300 mL full cream cow's milk, 100 g sugar, 20 g oil, 20 mL electrolyte/mineral solution, and water to 1000 mL.

<sup>c</sup>This lower-osmolality formula may be helpful for children with dysentery or persistent diarrhea. Cook for 4 min.

<sup>d</sup>A comparable F100 can be made from 110 g dried whole milk, 50 g sugar, 30 g oil, 20 mL electrolyte/mineral solution, and water to 1000 mL; or from 880 mL full cream cow's milk, 75 g sugar, 20 g oil, 20 mL electrolyte/mineral solution, and water to 1000 mL.

---

Table 46-11  Recipe for Rehydration Solution for Malnutrition (ReSoMal)

<table>
<thead>
<tr>
<th>INGREDIENT</th>
<th>AMOUNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>2 L</td>
</tr>
<tr>
<td>WHO-ORS</td>
<td>One 1-L sachet&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sucrose</td>
<td>50 g</td>
</tr>
<tr>
<td>Electrolyte/mineral solution&lt;sup&gt;+&lt;/sup&gt;</td>
<td>mL</td>
</tr>
</tbody>
</table>

ReSoMal contains 37.5 mmol sodium and 40 mmol potassium/L.

<sup>+</sup>Sachet contains 2.6 g sodium chloride, 2.9 g trisodium citrate, 1.5 g potassium chloride, 13.5 g glucose.

<sup>+</sup>See Table 46-12 for recipe, or use commercially available therapeutic Combined Mineral Vitamin mix (CMV).

Table 46-12  Recipe for Concentrated Electrolyte/Mineral Solution<sup>+</sup>

<table>
<thead>
<tr>
<th>INGREDIENT</th>
<th>g</th>
<th>mol/20 mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium chloride: KCl</td>
<td>224.0</td>
<td>24 mmol</td>
</tr>
<tr>
<td>Tripotassium citrate</td>
<td>81.0</td>
<td>2 mmol</td>
</tr>
<tr>
<td>Magnesium chloride: MgCl&lt;sub&gt;2&lt;/sub&gt;·6H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>76.0</td>
<td>3 mmol</td>
</tr>
<tr>
<td>Zinc acetate: Zn acetate·2H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>8.2</td>
<td>300 µmol</td>
</tr>
<tr>
<td>Copper sulfate: CuSO&lt;sub&gt;4&lt;/sub&gt;·5H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>1.4</td>
<td>45 µmol</td>
</tr>
<tr>
<td>Water: make up to</td>
<td>2500 mL</td>
<td></td>
</tr>
</tbody>
</table>

Add 20 mL when preparing 1 L of feed or ReSoMal.

<sup>+</sup>Make fresh each month. Use cooled boiled water.

unlimited amounts should be given of a high-energy, high-protein milk formula such as F100 (100 kcal and 3 g protein per 100 mL), or ready-to-use therapeutic food (RUTF), or family foods modified to have comparable energy and protein contents.

To make the transition, for 2 days replace F75 with an equal volume of F100 and then increase each successive feed by 10 mL, until some feed remains uneaten (usually at around 200 mL/kg/day).

After the transition, give 150-220 kcal/kg/day and 4-6 g protein/kg/day and continue to give potassium, magnesium, and micronutrients. Add iron (3 mg/kg/day). If breastfed, encourage continued breastfeeding.

Children with severe malnutrition have developmental delays, so loving care, structured play, and sensory stimulation during and after treatment are essential to aid recovery of brain function.

**Community-based treatment:** Many children with severe acute malnutrition can be identified in their communities before medical complications arise. If these children have a good appetite and are clinically well, they can be rehabilitated at home through community-based therapeutic care, which has the added benefit of reducing their exposure to nosocomial infections and providing continuity of care after
recovery. It also reduces the time caregivers spend away from home and their opportunity costs, and can be cost-effective for health services.

Figure 46-7 shows the criteria for inpatient versus outpatient care. To maximize coverage and compliance, community-based therapeutic care has 4 main elements: community mobilization and sensitization; active case-finding; therapeutic care; and follow-up after discharge.

Community-based therapeutic care comprises steps 8-10, plus a broad-spectrum antibiotic (step 5). RUTF is usually provided, especially in times of food shortage. RUTF is specially designed for rehabilitating children with severe acute malnutrition at home. It is high in energy and protein and has electrolytes and micronutrients added. The most widely used RUTF is a thick paste that contains milk powder, peanuts, vegetable oil, and sugar. Pathogens cannot grow in it because of its low moisture content. Hospitalized children who have completed steps 1-7 and the transition can be transferred to community-based care for completion of their rehabilitation, thereby reducing their hospital stay to about 7-10 days.

Bibliography is available at Expert Consult.

### 46.1 Refeeding Syndrome

Robert M. Kliegman

Refeeding syndrome can complicate the acute nutritional rehabilitation of children who are undernourished from any cause (Table 46-13). Refeeding syndrome is rare when the WHO recommendations for the treatment of malnutrition are followed (see Chapter 46); however, it may follow overly aggressive enteral or parenteral alimentation. Malnutrition usually has normal serum electrolytes but is associated with intracellular electrolyte depletion. When excessive carbohydrates are administered, the resultant increase in serum insulin levels may produce hypokalemia, hypophosphatemia, and hypomagnesemia. The hallmark of refeeding syndrome is the development of severe hypophosphatemia after the cellular uptake of phosphate during the first week of starting to refeed. Serum phosphate levels of $\leq 0.5$ mmol/L can produce weakness, rhabdomyolysis, neutrophil dysfunction, cardiopulmonary failure, arrhythmias, seizures, altered level of consciousness, or sudden death. Phosphate levels should be monitored during refeeding, and if they are low, phosphate should be administered during refeeding to treat severe hypophosphatemia (see Chapter 55.6).

<table>
<thead>
<tr>
<th>HYPOPHOSPHATEMIA</th>
<th>HYPOKALEMIA</th>
<th>HYPMAGNESEMIA</th>
<th>VITAMIN/THIAMINE DEFICIENCY</th>
<th>SODIUM RETENTION</th>
<th>HYPERGLYCEMIA</th>
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<td>Cardiac</td>
<td>Cardiac</td>
<td>Cardiac</td>
<td>Encephalopathy</td>
<td>Fluid overload</td>
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<td>Lactic acidosis</td>
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<td>Respiratory Failure</td>
<td>Neurologic</td>
<td>Death</td>
<td>Cardiac compromise</td>
<td>Respiratory</td>
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<td>Respiratory</td>
<td>Neurologic</td>
<td>Weakness</td>
<td>Failure</td>
<td>Other</td>
<td>Failure</td>
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<td>Impaired diaphragm contractility</td>
<td>Weakness</td>
<td>Tremor</td>
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<td>Other</td>
<td>Ketoacidosis</td>
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<td>Dyspnea</td>
<td>Paralysis</td>
<td>Tetany</td>
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<td>Coma</td>
<td>Coma</td>
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<td>Respiratory failure</td>
<td>Gastrointestinal Nausea</td>
<td>Seizures</td>
<td></td>
<td>Gastrointestinal</td>
<td>Dehydration</td>
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<td>Neurologic</td>
<td>Vomiting</td>
<td>Altered mental status</td>
<td></td>
<td>Nausea</td>
<td>Impaired immune function</td>
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<td>Paresthesia</td>
<td>Constipation</td>
<td>Coma</td>
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<td>Vomiting</td>
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<td>Weakness</td>
<td>Muscular</td>
<td>Muscle necrosis</td>
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<td>Confusion</td>
<td>Rhabdomyolysis</td>
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<td>Other</td>
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<td>Disorientation</td>
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<td>Death</td>
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<td>Refractory</td>
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<td>Lethargy</td>
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<td>hypokalemia and hypocalcemia</td>
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<td>Areflexic paralysis</td>
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<td>Death</td>
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<tr>
<td>Seizures</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Coma</td>
<td></td>
<td></td>
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<tr>
<td>Hematologic</td>
<td></td>
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<tr>
<td>Leukocyte dysfunction</td>
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<tr>
<td>Hemolysis</td>
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<tr>
<td>Thrombocytopenia</td>
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<tr>
<td>Other</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
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</tbody>
</table>

Bibliography
Obesity is an important pediatric public health problem associated with risk of complications in childhood and increased morbidity and mortality throughout adult life.

**EPIDEMIOLOGY**

Obesity is a global public health problem, sparing only dramatically poor regions with chronic food scarcity such as sub-Saharan Africa and Haiti. In 2008, according to the World Health Organization, more than 1.4 billion persons ≥20 yr old were overweight or obese. In the United States, 36% of adults are obese, and an additional 35% of adults are overweight. In children, the prevalence of obesity increased 300% over approximately 40 yr. The National Health and Nutrition Examination Survey, 2009-2010, found 32% of children, 2-19 yr old to be overweight or obese, and 17% in the obese range. Children’s risk varies significantly by race/ethnicity. In 2009-2010, 24% of non-Hispanic Black, 21% of Hispanic, and >20% of American Indian/Alaskan Native children and adolescents were obese compared to 14% of white children. Across all racial groups, higher maternal education confers protection against childhood obesity.

Parental obesity correlates with a higher risk for obesity in their children. Prenatal factors including high preconceptual weight, gestational weight gain, high birth weight, and maternal smoking are associated with increased risk for later obesity. Paradoxically, intrauterine growth restriction with early infant catch-up growth is associated with the development of central adiposity and adult-onset cardiovascular risk. Breastfeeding is only modestly protective for obesity. Infants with high levels of negative reactivity (temperament) are at risk for obesity. Better self-regulation is protective.

**BODY MASS INDEX**

Obesity or increased adiposity is defined using the body mass index (BMI), which is an excellent proxy for more direct measurement of body fat. BMI = weight in kg/(height in meters)^2. Adults with a BMI ≥30 meet the criterion for obesity, and those with a BMI 25-30 fall in the overweight range. During childhood, levels of body fat change beginning with high adiposity during infancy. Body fat levels decrease for approximately 5.5 yr until the period called adiposity rebound, when body fat is typically at the lowest level. Adiposity then increases until early adulthood (Fig. 47-1). Consequently, obesity and overweight are defined using BMI percentiles; children ≥2 yr old with a BMI ≥95th percentile meet the criterion for obesity, and those with a BMI between the 85th and 95th percentiles fall in the overweight range.

**ETIOLOGY**

Humans have the capacity to store energy in adipose tissue, allowing improved survival in times of famine. Furthermore, humans innately prefer sweet and salty foods and reject bitter flavors. Many vegetables are bitter. These preferences probably reflect evolutionary adaptations to avoid consuming toxic plants. Nonetheless, repeated exposure to healthy foods promotes their acceptance and liking, especially in early life. Simplistically, obesity results from an imbalance of caloric intake and energy expenditure. Even incremental but sustained caloric excess results in excess adiposity. Individual adiposity is the result of a complex interplay among genetically determined body habitus, appetite, nutritional intake, physical activity, and energy expenditure. Environmental factors determine levels of available food, preferences for types of foods, levels of physical activity, and preferences for types of activities.

**Environmental Changes**

Over the last 4 decades, the food environment has changed dramatically. Changes in the food industry relate in part to social changes, as extended families have become more dispersed. Fewer families routinely prepare meals. Foods are increasingly prepared by a food industry, with high levels of calories, simple carbohydrates, and fat. The price of many foods has declined relative to the family budget. These changes, in combination with marketing pressure, have resulted in larger portion sizes and increased snacking between meals. The increased consumption of high-carbohydrate beverages, including sodas, sport drinks, fruit punch, and juice, adds to these factors.

One-third of U.S. children consume fast food daily. A typical fast food meal can contain 2000 kcal and 84 g of fat. Many children consume 4 servings of high-carbohydrate beverages per day, resulting in an additional 560 kcal of low nutritional value. Sweetened beverages have been linked to increased risk for obesity because children who drink high amounts of sugar do not consume less food. The dramatic increase in the use of high-fructose corn syrup to sweeten beverages and prepared foods is another important environmental change, leading to availability of inexpensive calories.

Since World War II, levels of physical activity in children and adults have declined. Changes in the built environment have resulted in more reliance on cars and decreased walking. Work is increasingly sedentary, and many sectors of society do not engage in physical activity during leisure time. For children, budgetary constraints and pressure for academic performance have led to less time devoted to physical education in schools. Perception of poor neighborhood safety is another factor that can lead to lower levels of physical activity when children are required to stay indoors. The advent of television, computers, and video games has resulted in opportunities for sedentary activities that do not burn calories.

Changes in another health behavior, sleep, might also contribute. Over the last 4 decades, children and adults have decreased the amount of time spent sleeping. Reasons for these changes may relate to increased time at work, increased time watching television, and a generally faster pace of life. Chronic partial sleep loss can increase risk for weight gain and obesity, with the impact possibly greater in children than in adults. In studies of young, healthy, lean men, short sleep duration was associated with decreased leptin levels and increased ghrelin levels, along with increased hunger and appetite. Sleep debt also results in decreased glucose tolerance and insulin sensitivity related to alterations in glucocorticoids and sympathetic activity. Some effects of sleep debt might relate to orexins, peptides synthesized in the lateral hypothalamus that can increase feeding, arousal, sympathetic activity, and/or neuropeptide Y activity.

**Genetics**

Genetic determinants also have a role in individual susceptibility to obesity (Table 47-1). Findings from genome-wide association studies explain a very small portion of interindividual variability in obesity. One important example, the FTO gene at 16q12, is associated with adiposity in childhood, probably explained by increased energy intake (Table 47-1). Monogenic forms of obesity have also been identified, including MC4R deficiency, associated with early-onset obesity and food-seeking behavior. In addition, there are genetic conditions associated with obesity, such as Prader-Willi syndrome, which results from absence of paternally expressed imprinted genes in the 15q11.2–q13 region. Prader-Willi syndrome is characterized by insatiable appetite and food seeking. Epigenetic environmental modification of genes may have a role in the development of obesity, especially during fetal and early life.

**Endocrine and Neural Physiology**

Monitoring of “stored fuels” and short-term control of food intake (appetite and satiety) occurs through neuroendocrine feedback loops linking adipose tissue, the gastrointestinal tract, and the central
2 to 20 years: Boys
Body mass index-for-age percentiles

<table>
<thead>
<tr>
<th>Date</th>
<th>Age</th>
<th>Weight</th>
<th>Stature</th>
<th>BMI*</th>
<th>Comments</th>
</tr>
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</tbody>
</table>

*To Calculate BMI: Weight (kg) / Stature (cm) ^ 2 or Weight (lb) / [Stature (in) ^ 2 * 703]

Figure 47-1 Body mass index (BMI)-for-age profiles for boys and men (A) and girls and women (B). Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000). See www.cdc.gov/growthcharts
2 to 20 years: Girls
Body mass index-for-age percentiles

*To Calculate BMI: Weight (kg) = Stature (cm) x Stature (cm) x 10,000
or Weight (lb) = Stature (in) x Stature (in) x 703

Published May 30, 2000 (modified 10/16/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

Figure 47-1, cont’d
nervous system (Fig. 47-2). Gastrointestinal hormones, including cho-
lecystokinin, glucagon-like peptide-1, peptide YY, and vagal neuronal
feedback promote satiety. Ghrelin stimulates appetite. Adipose tissue
provides feedback regarding energy storage levels to the brain through
hormonal release of adiponectin and leptin. These hormones act on
the arcuate nucleus in the hypothalamus and on the solitary tract
nucleus in the brainstem and, in turn, activate distinct neuronal net-
works. Adipocytes secrete adiponectin into the blood, with reduced
levels in response to obesity and increased levels in response to fasting.
Reduced adiponectin levels are associated with lower insulin sensitivity
and adverse cardiovascular outcomes. Leptin is directly involved in
satiety, as low leptin levels stimulate food intake and high leptin levels
inhibit hunger in animal models and in healthy human volunteers.
Adiposity correlates to serum leptin levels among children and adults,
with the direction of effect remaining unclear.

Numerous neuropeptides in the brain, including peptide YY, agouti-
related peptide, and orexin, appear to affect appetite stimulation,
whereas melanocortins and α-melanocortin–stimulating hormone are
involved in satiety. The neuroendocrine control of appetite and weight
involves a negative-feedback system, balanced between short-term
control of appetite and long-term control of adiposity (including
leptin). Peptide YY reduces food intake via the vagal–brainstem–
hypothalamic pathway. Developmental changes in peptide YY are
evident as infants have higher levels of peptide YY than school-age
children even though this does not happen in adults. In addition,
patients homozygous for the FTO obesity risk allele demonstrate poor
regulation of the orexigenic hormone acyl-ghrelin and have poor post-
prandial appetite suppression.

### Table 47-1  Endocrine and Genetic Causes of Obesity

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>SYMPTOMS</th>
<th>LABORATORY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ENDOCRINE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cushing syndrome</td>
<td>Central obesity, hirsutism, moon face, hypertension</td>
<td>Dexamethasone suppression test</td>
</tr>
<tr>
<td>GH deficiency</td>
<td>Short stature, slow linear growth</td>
<td>Evoked GH response, IGF-1</td>
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<td>Hyperinsulinism</td>
<td>Nesiobiostasis, pancreatic adenoma, hypoglycemia, Mauriac syndrome</td>
<td>Insulin level</td>
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<td>Hypothyroidism</td>
<td>Short stature, weight gain, fatigue, constipation, cold intolerance, myxedema</td>
<td>TSH, FT₄</td>
</tr>
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<td>Pseudohypoparathyroidism</td>
<td>Short metacarpals, subcutaneous calcifications, dysmorphic facies, mental retardation, short stature, hypocalcemia, hyperphosphatemia</td>
<td>Urine cAMP after synthetic PTH infusion</td>
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<tr>
<td><strong>GENETIC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alstrom syndrome</td>
<td>Cognitive impairment, retinitis pigmentosa, diabetes mellitus, hearing loss, hypogonadism, retinal degeneration</td>
<td>ALMS1 gene</td>
</tr>
<tr>
<td>Bardet-Biedl syndrome</td>
<td>Retinitis pigmentosa, renal abnormalities, polydactyly, hypogonadism</td>
<td>BBS1 gene</td>
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<td>Biemond syndrome</td>
<td>Cognitive impairment, ir coloboma, hypogonadism, polydactyly</td>
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<td>Carpenter syndrome</td>
<td>Polydactyly, syndactyly, cranial synostosis, mental retardation</td>
<td>Deletion 9q34</td>
</tr>
<tr>
<td>Cohen syndrome</td>
<td>Mid-childhood-onset obesity, short stature, prominent maxillary incisors, hypotonia, mental retardation, microcephaly, decreased visual activity</td>
<td>Mutations in the RA823 gene, located on chromosome 6 in humans</td>
</tr>
<tr>
<td>Deletion 9q34</td>
<td>Early-onset obesity, mental retardation, brachycephaly, synophrys, prognathism, behavior and sleep disturbances</td>
<td>Trisomy 21</td>
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<tr>
<td>Down syndrome</td>
<td>Short stature, dysmorphic facies, mental retardation</td>
<td>Gene mutation on chromosome 6q</td>
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<td>ENPP1 gene mutations</td>
<td>Insulin resistance, childhood obesity</td>
<td>Homozygous for FTO AA allele</td>
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<td>Fröhlich syndrome</td>
<td>Hypothalamic tumor</td>
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<td>FTO gene polymorphism</td>
<td>Dysregulation of orexigenic hormone acyl-ghrelin, poor postprandial appetite suppression</td>
<td>MC4R mutation</td>
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<td>Leptin or leptin receptor gene deficiency</td>
<td>Early-onset severe obesity, infertility (hypogonadotrophic hyponadism)</td>
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<td>Melanocortin 4 receptor gene mutation</td>
<td>Early-onset severe obesity, increased linear growth, hyperphagia, hyperinsulinemia</td>
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<td>Prader-Willi Syndrome</td>
<td>Neonatal hypotonia, slow infant growth, small hands and feet, mental retardation, hypogonadism, hypophagia leading to severe obesity, paradoxically elevated ghrelin</td>
<td>Partial deletion of chromosome 15 or loss of paternally expressed genes</td>
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<td>Proopiomelanocortin deficiency</td>
<td>Obesity, red hair, adrenal insufficiency, hyperproinsulinemia</td>
<td>Loss-of-function mutations of the POMC gene</td>
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<tr>
<td>Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD)</td>
<td>Often confused with congenital central hypoventilation syndrome (CHHS), presentation ≥ 1.5 yr with weight gain, hyperphagia, hypoventilation, cardiac arrest, central diabetes insipidus, hypothyroidism, growth hormone deficiency, pain insensitivity, hypothermia, precocious puberty, neural crest tumors</td>
<td>Unknown genes</td>
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<tr>
<td>Turner syndrome</td>
<td>Ovarian dysgenesis, lymphedema, web neck, short stature, cognitive impairment</td>
<td>XO chromosome</td>
</tr>
</tbody>
</table>

- cAMP, cyclic adenosine monophosphate; FT₄, free thyroxine; GH, growth hormone; IGF, insulin-like growth factor; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone.
Chapter 47 • Overweight and Obesity

Overweight and Obesity

Figure 47-2 Regulation of energy homeostasis by the brain–adipose tissue–intestinal axis. Leptin stimulates hypothalamic anorexigenic and inhibits orexigenic neurons. Adiponectin stimulates hepatic, and muscle glucose utilization and increases insulin sensitivity, while interleukin-6 (IL-6) contributes to adipose tissue, muscle and hepatic insulin resistance. Peptide YY (PYY) inhibits orexigenic and glucagon-like peptide 1 (GLP-1) stimulates anorexigenic hypothalamic neurons. GLP-1 also augments glucose stimulated pancreatic insulin secretion and suppresses glucagon secretion. Insulin stimulates adipose tissue and muscle glucose uptake, enhances lipogenesis, suppresses hepatic glucose production, and has an inhibitory effect on the hypothalamic anorexigenic system. Ghrelin stimulates the orexigenic hypothalamic pathways. (Modified from Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: Williams Textbook of Endocrinology, ed 12, Philadelphia, 2011, Saunders. Fig. 35-1.)

**COMORBIDITIES**

Complications of pediatric obesity occur during childhood and adolescence and persist into adulthood. An important reason to prevent and treat pediatric obesity is the increased risk for morbidity and mortality later in life. The Harvard Growth Study found that boys who were overweight during adolescence were twice as likely to die from cardiovascular disease as those who had normal weight. More immediate comorbidities include type 2 diabetes, hypertension, hyperlipidemia, and nonalcoholic fatty liver disease (Table 47-2). Insulin resistance increases with increasing adiposity and independently affects lipid metabolism and cardiovascular health. The metabolic syndrome (central obesity, hypertension, glucose intolerance, and hyperlipidemia) increases risk for cardiovascular morbidity and mortality. Nonalcoholic fatty liver disease (NAFLD) occurs in 10-25% of obese...
### Table 47-2  Obesity-Associated Comorbidities

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>POSSIBLE SYMPTOMS</th>
<th>LABORATORY CRITERIA</th>
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</thead>
<tbody>
<tr>
<td><strong>CARDIOVASCULAR</strong></td>
<td>Dyslipidemia, Hypertension</td>
<td>HDL &lt;40, LDL &gt;130, total cholesterol &gt;200, SBP &gt;95% for sex, age, height</td>
</tr>
<tr>
<td><strong>ENDOCRINE</strong></td>
<td>Type 2 diabetes mellitus, Metabolic syndrome, Polycystic ovary syndrome</td>
<td>Acanthosis nigrians, polyuria, polydipsia, Central adiposity, insulin resistance, dyslipidemia, hypertension, glucose intolerance, Irregular menses, hirsutism, acne, insulin resistance, hyperandrogenemia</td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL</strong></td>
<td>Gallbladder disease, Nonalcoholic fatty liver disease (NAFLD)</td>
<td>Abdominal pain, vomiting, jaundice, Hepatomegaly, abdominal pain, dependent edema, ↑ transaminases</td>
</tr>
<tr>
<td><strong>NEUROLOGIC</strong></td>
<td>Pseudotumor cerebri, Migraines</td>
<td>Headaches, vision changes, papilledema, Hemicrania, headaches</td>
</tr>
<tr>
<td><strong>ORTHEPODIC</strong></td>
<td>Blount disease (tibia vara), Musculoskeletal problems, Slipped capital femoral epiphysis</td>
<td>Severe bowing of tibia, knee pain, limp, Back pain, joint pain, frequent strains or sprains, hip pain, groin pain, leg bowing, Hip pain, knee pain, limp, decreased mobility of hip</td>
</tr>
<tr>
<td><strong>PSYCHOLOGICAL</strong></td>
<td>Behavioral complications</td>
<td>Anxiety, depression, low self-esteem, disordered eating, signs of depression, worsening school performance, social isolation, problems with bullying or being bullied</td>
</tr>
<tr>
<td><strong>PULMONARY</strong></td>
<td>Asthma, Obstructive sleep apnea</td>
<td>Shortness of breath, wheezing, coughing, exercise intolerance, Snoring, apnea, restless sleep, behavioral problems</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, computed tomography; FSH, follicle-stimulating hormone; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LH, luteinizing hormone; MRI, magnetic resonance imaging; Peds QL, Pediatric Quality of Life Inventory; SBP, systolic blood pressure.

adolescents. NAFLD is now the most common chronic liver disease in U.S. children and adolescents. It can present with advanced fibrosis or nonalcoholic steatohepatitis and may result in cirrhosis and hepatocellular carcinoma. Insulin resistance is commonly associated. Furthermore, NAFLD is independently associated with increased risk of cardiovascular disease.

Obesity may also be associated with chronic inflammation. Adipocytokines, a peptide with antiinflammatory properties, occurs in reduced levels in obese patients as compared to insulin-sensitive, lean persons. Low adiponectin levels correlate with elevated levels of free fatty acids and plasma triglycerides as well as a high BMI, and high adiponectin levels correlate with peripheral insulin sensitivity. Adipocytokines secrete peptides and cytokines into the circulation, and proinflammatory peptides such interleukin (IL)-6 and tumor necrosis factor-α (TNF-α) occur in higher levels in obese patients. Specifically, IL-6 stimulates production of C-reactive protein in the liver. C-reactive protein is a marker of inflammation and might link obesity, coronary disease, and subclinical inflammation.

Some complications of obesity are mechanical, including obstructive sleep apnea and orthopedic complications. Orthopedic complications include Blount disease and slipped femoral capital epiphysis (see Chapters 677, 678, 4).

Mental health problems can coexist with obesity, with the possibility of bidirectional effects. These associations are modified by gender, ethnicity, and socioeconomic status. Self-esteem may be lower in obese adolescent girls compared to nonobese peers. Some studies have found an association between obesity and adolescent depression. There is considerable interest in the cooccurrence of eating disorders and obesity.

### IDENTIFICATION

Overweight and obese children are often identified as part of routine medical care, and the child and family may be unaware that the child has increased adiposity. They may be unhappy with the medical provider for raising this issue and respond with denial or apparent lack of concern. It is often necessary to begin by helping the family understand the importance of healthy weight for current and future health, especially because intervention requires considerable effort by the child and the family. Forging a good therapeutic relationship is important, because obesity intervention requires a chronic disease management approach. Successful resolution of this problem necessitates considerable family and child effort over an extended period in order to change eating and activity behaviors.

### EVALUATION

The evaluation of the overweight or obese child begins with examination of the growth chart for weight, height, and BMI trajectories; consideration of possible medical causes of obesity; and detailed
exploration of family eating, nutritional, and activity patterns. A complete pediatric history is used to uncover comorbid disorders. The family history focuses on the adiposity of other family members and the family history of obesity-associated disorders. The physical examination adds data that can lead to important diagnoses. Laboratory testing is guided by the need to identify comorbid conditions.

Examination of the growth chart reveals the severity, duration, and timing of obesity onset. Children who are overweight (BMI in the 85th-95th percentile) are less likely to have developed comorbid conditions than those who are obese (BMI ≥95th percentile). Those with a BMI ≥99th percentile are even more likely to have coexisting medical problems. Once obesity severity is determined, the BMI trajectory is examined to elucidate when the child became obese. Several periods during childhood are considered sensitive periods or times of increased risk for developing obesity, including infancy, adiposity rebound (when body fat is lowest at approximately age 5.5 yr), and adolescence. An abrupt change in BMI might signal the onset of a medical problem or a period of family or personal stress for the child. Examination of the weight trajectory can further expand understanding of how the problem developed. A young child might exhibit high weight and high height because linear growth can increase early in childhood if a child consumes excess energy. At some point, the weight percentile exceeds the height percentile and the child’s BMI climbs into the obese range. Another example is a child whose weight rapidly increases when she reduces her activity level and consumes more meals away from home. Examination of the height trajectory can reveal endocrine problems, which often occur with slowing of linear growth.

Consideration of possible medical causes of obesity is essential, even though endocrine and genetic causes are rare (see Table 47-1). Growth hormone deficiency, hypothyroidism, and Cushing syndrome are examples of endocrine disorders that can lead to obesity. In general, these disorders manifest with slow linear growth. Because children who consume excessive amounts of calories tend to experience accelerated linear growth, short stature warrants further evaluation. Genetic disorders associated with obesity can have coexisting dysmorphic features, cognitive impairment, vision and hearing abnormalities, or short stature. In some children with congenital disorders such as myelodysplasia or muscular dystrophy, lower levels of physical activity can lead to secondary obesity. Some medications can cause excessive appetite and hyperphagia, resulting in obesity. Atypical antipsychotic medications often have this dramatic side effect. Rapid weight gain in a child or adolescent taking one of these medications might require a discontinuation of that medication. Poor linear growth and rapid changes in weight gain are indications for evaluation of possible medical causes.

Exploration of family eating and nutritional and activity patterns begins with a description of regular meal and snack times and family habits for walking, bicycle riding, active recreation, television, computer, and video game time. It is useful to request a 24-hr dietary recall with special attention to intake of fruits, vegetables, and water, as well as high-calorie foods and high-carbohydrate beverages. When possible, evaluation by a nutritionist is extremely helpful. This information will form the basis for incremental changes in eating behavior, caloric intake, and physical activity during the intervention.

Initial assessment of the overweight or obese child includes a complete review of bodily systems focusing on the possibility of comorbid conditions (see Table 47-2). Developmental delay and visual and hearing impairment can be associated with genetic disorders. Difficulty sleeping, snoring, or daytime sleepiness suggests the possibility of sleep apnea. Abdominal pain might suggest NAFLD. Symptoms of polypnea, nocturia, or polydipsia may be the result of type 2 diabetes. Hip or knee pain can be caused by secondary orthopedic problems, including Blount disease and slipped capital femoral epiphysis. Irregular menses or signs of insulin resistance should also be evaluated with a fasting plasma glucose test. Other laboratory testing should be guided by history or physical examination findings.

**INTERVENTION**

There is evidence that some interventions result in modest but significant and sustained improvement in body mass. Based on behavior change theories, treatment includes specifying target behaviors, self-monitoring, goal setting, stimulus control, and promotion of self-efficacy and self-management skills. Behavior changes associated with improving BMI include drinking lower quantities of sugar-sweetened beverages, consuming higher-quality diets, increasing exercise, watching less TV, and self-weighing. Most successful interventions have been family based and take into account the child’s developmental age. “Parent-only” treatment can be as effective as “parent–child” treatment. Because obesity is multifactorial, not all children and adolescents will respond to the same approach. For example, “loss-of-control” eating, associated with weight gain and obesity, predicts poor outcome in response to family-based treatment. Furthermore, clinical-treatment programs are expensive and not widely available. Therefore there is interest in novel approaches including Internet-based treatments and guided self-help.

It is important to begin with clear recommendations about appropriate caloric intake for the obese child (Table 47-4). Working with a dietitian is very helpful. Meals should be based on fruits, vegetables, whole grains, lean meat, fish, and poultry. Prepared foods should be chosen for their nutritional value, with attention to calories and fat. Foods that provide excessive calories and low nutritional value should be reserved for infrequent treats.
Weight-reduction diets in adults generally do not lead to sustained weight loss. Therefore, the focus should be on changes that can be maintained for life. Attention to eating patterns is helpful. Families should be encouraged to plan family meals, including breakfast. It is almost impossible for a child to make changes in nutritional intake and eating patterns if other family members do not make the same changes. Dietary needs also change developmentally, as adolescents require greatly increased calories during their growth spurts, and adults who lead inactive lives need fewer calories than active and growing children.

Psychological strategies are helpful. The “traffic light” diet groups foods into those that can be consumed without any limitations (green), in moderation (yellow), or reserved for infrequent treats (red) (Table 47-5). The concrete categories are very helpful to children and families. This approach can be adapted to any ethnic group or regional cuisine. Motivational interviewing begins with assessing how ready the patient is to make important behavioral changes. The professional then engages the patient in developing a strategy to take the next step toward the ultimate goal of healthy nutritional intake. This method allows the professional to take the role of a coach, helping the child and family reach their goals. Other behavioral approaches include family rules about where food may be consumed; for example, “not in the bedroom.”

Increasing physical activity without decreasing caloric intake is unlikely to result in weight loss. Nonetheless, it can increase aerobic fitness and decrease percent body fat even without weight loss. Therefore, increasing physical activity can decrease risk for cardiovascular disease, improve well-being, and contribute to weight loss. Increased physical activity can be accomplished by walking to school, engaging in physical activity during leisure time with family and friends, or enrolling in organized sports. Children are more likely to be active if their parents are active. Just as family meals are recommended, family physical activity is recommended.

Active pursuits can replace more sedentary activities. The American Academy of Pediatrics recommends that screen time be restricted to no more than 2 hr/day for children >2 yr old and that children <2 yr old not watch television. Television watching is often associated with eating, and many highly caloric food products are marketed directly to children during child-oriented television programs.

Pediatric providers should assist families to develop goals to change nutritional intake and physical activity. They can also provide the child and family with needed information. The family should not expect immediate lowering of BMI percentile related to behavioral changes but can instead count on a gradual decrease in the rate of BMI percentile increase until it stabilizes, followed by a gradual decrease in BMI percentile. Referral to multidisciplinary, comprehensive pediatric weight-management programs is ideal for obese children whenever possible.

There is no effective pharmacotherapy resulting in reversal of excess adiposity in children and adolescents. Available medications result in

### Table 47-3 Normal Laboratory Values for Recommended Tests

<table>
<thead>
<tr>
<th>LABORATORY TEST</th>
<th>NORMAL VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>&lt;110 mg/dL</td>
</tr>
<tr>
<td>Insulin</td>
<td>&lt;15 mIU/L</td>
</tr>
<tr>
<td>Hemoglobin A₁c</td>
<td>&lt;5.7%</td>
</tr>
<tr>
<td>AST (age 2-8 yr)</td>
<td>&lt;58 U/L</td>
</tr>
<tr>
<td>AST (age 9-15 yr)</td>
<td>&lt;46 U/L</td>
</tr>
<tr>
<td>AST (age 15-18 yr)</td>
<td>&lt;35 U/L</td>
</tr>
<tr>
<td>ALT</td>
<td>&lt;35 U/L</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>&lt;170 mg/dL</td>
</tr>
<tr>
<td>LDL</td>
<td>&lt;110 mg/dL</td>
</tr>
<tr>
<td>HDL</td>
<td>&gt;45 mg/dL</td>
</tr>
<tr>
<td>Triglycerides (age 0-9 yr)</td>
<td>&lt;75 mg/dL</td>
</tr>
<tr>
<td>Triglycerides (age 10-19 yr)</td>
<td>&lt;90 mg/dL</td>
</tr>
</tbody>
</table>

AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDL, low-density lipoprotein; HDL, high-density lipoprotein.


### Table 47-4 Recommended Caloric Intake Designated by Age and Gender

<table>
<thead>
<tr>
<th>LIFE-STAGE GROUP</th>
<th>AGE (yr)</th>
<th>RELATIVELY SEDENTARY LEVEL OF ACTIVITY (kcal)</th>
<th>MODERATE LEVEL OF ACTIVITY (kcal)</th>
<th>ACTIVE (kcal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child</td>
<td>2-3</td>
<td>1,000</td>
<td>1,000-1,400</td>
<td>1,000-1,400</td>
</tr>
<tr>
<td>Female</td>
<td>4-8</td>
<td>1,200</td>
<td>1,400-1,600</td>
<td>1,400-1,800</td>
</tr>
<tr>
<td></td>
<td>9-13</td>
<td>1,600</td>
<td>1,600-2,000</td>
<td>1,800-2,200</td>
</tr>
<tr>
<td></td>
<td>14-18</td>
<td>1,800</td>
<td>2,000</td>
<td>2,400</td>
</tr>
<tr>
<td>Male</td>
<td>4-8</td>
<td>1,400</td>
<td>1,400-1,600</td>
<td>1,600-2,000</td>
</tr>
<tr>
<td></td>
<td>9-13</td>
<td>1,800</td>
<td>1,800-2,200</td>
<td>2,000-2,600</td>
</tr>
<tr>
<td></td>
<td>14-18</td>
<td>2,200</td>
<td>2,400-2,800</td>
<td>2,800-3,200</td>
</tr>
</tbody>
</table>


### Table 47-5 Traffic Light Diet Plan

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>GREEN LIGHT FOODS</th>
<th>YELLOW LIGHT FOODS</th>
<th>RED LIGHT FOODS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality</td>
<td>Low-calorie, high-fiber, low-fat, nutrient-dense</td>
<td>Nutrient-dense, but higher in calories and fat</td>
<td>High in calories, sugar, and fat</td>
</tr>
<tr>
<td>Types of food</td>
<td>Fruits, vegetables</td>
<td>Lean meats, dairy, starches, grains</td>
<td>Fatty meats, sugar, sugar-sweetened beverages, fried foods</td>
</tr>
<tr>
<td>Quantity</td>
<td>Unlimited</td>
<td>Limited</td>
<td>Infrequent or avoided</td>
</tr>
</tbody>
</table>
modest weight loss or BMI improvement even when combined with behavioral interventions. Various classes of drugs are of interest, including those that decrease energy intake or act centrally as anorexigens, those that affect the availability of nutrients through intestinal or renal tubular reabsorption, and those that affect metabolism. The only U.S. Food and Drug Administration (FDA)-approved medication for obesity in children <16 yr old is orlistat, which decreases absorption of fat, resulting in modest weight loss. Complications include ileus, oily stools, and spotting. This agent offers little benefit to severely obese adolescents. Because there are multiple redundant neural mechanisms that act to protect body weight, promoting weight loss is extremely difficult. For this reason, there is considerable interest in combining therapies that simultaneously target multiple weight-regulating pathways. One example, approved for adults, combines phentermine, a noradrenergic agent, with topiramate, a γ-aminobutyric acid (GABA)-ergic medication. This combination resulted in a mean 10.2-kg weight loss compared to 1.4 kg in the placebo group. Side effects are common and include dry mouth, constipation, paresthesias, insomnia, and cognitive dysfunction. Another promising example is the combination of amylin (decreases food intake and slows gastric emptying) with leptin (which has no anorexigenic effects when given alone). This combination requires injection and is in clinical trials in adults. Another FDA approved (for adults) drug is lorcaserin, a selective serotonin 2C receptor agonist. Establishing long-term safety and tolerability in children is a challenge as medications of interest have central nervous system effects or interfere with absorption of nutrients; teratologic effects must be considered for use in adolescent girls.

In some cases, it is reasonable to refer adolescents for evaluation for bariatric surgery. The American Pediatric Surgical Association Guidelines recommends that surgery be considered only in children with complete or near-complete skeletal maturity, a BMI ≥40, and a medical complication resulting from obesity, after they have failed 6 mo of a multidisciplinary weight management program. Surgical approaches include the Roux-en-Y and the adjustable gastric band. In obese adults, bariatric surgery reduces the risk of developing type 2 diabetes mellitus. In obese adult patients with existing type 2 diabetes, bariatric surgery improves the control of diabetes.

PREVENTION

Prevention of child and adolescent obesity is essential for public health in the United States and most other countries (Table 47-6 and 47-7). Efforts by pediatric providers can supplement national- and community-level public health programs. The National Institutes of Health and Centers for Disease Control and Prevention recommend a variety of initiatives to combat the current obesigenic environment, including promotion of breastfeeding, access to fruits and vegetables, walkable communities, and 60 min/day of activity for children. The U.S. Department of Agriculture sponsors programs promoting 5.5 cups of fruits and vegetables per day. Incentives for the food industry to promote consumption of healthier foods should be considered. Marketing of unhealthy foods to children has begun to be regulated. We expect to see changes in federal food programs including commodity foods, the Women, Infant, and Children Supplemental Food Program, and school-lunch programs to meet the needs of today’s children.

Pediatric prevention efforts begin with careful monitoring of weight and BMI percentiles at healthcare maintenance visits. Attention to changes in BMI percentiles can alert the pediatric provider to increasing adiposity before the child becomes overweight or obese. All families should be counseled about healthy nutrition for their children because the current prevalence of overweight and obesity in adults is 65%. Therefore, approximately two-thirds of all children can be considered at risk for becoming overweight or obese at some time in their lives. Those who have an obese parent are at increased risk. Prevention efforts begin with promotion of exclusive breastfeeding for 6 mo and total breastfeeding for 12 mo. Introduction of infant foods at 6 mo should focus on cereals, fruits, and vegetables. Lean meats, poultry, and fish may be introduced later in the 1st year of life. Parents should be specifically counseled to avoid introducing highly sugared beverages and foods in the 1st year of life. Instead, they should expose their infants and young children to a rich variety of fruits, vegetables, grains, lean meats, poultry, and fish to facilitate acceptance of a diverse and healthy diet. Parenting matters, and authoritative parents are more likely to have children with a healthy weight than those who are authoritarian or permissive. Families who eat regularly scheduled meals together are less likely to have overweight or obese children. Child health professionals are able to address a child’s nutritional status and to provide expertise in child growth and development.

Child health professionals can also promote physical activity during regular healthcare maintenance visits. Parents who spend some of their leisure time in physical activity promote healthy weight in their children. Beginning in infancy, parents should be cognizant of their child’s developmental capability and need for physical activity. Because television, computer, and video game use can replace health-promoting physical activity, physicians should counsel parents to limit screen time for their children. Snacking during television watching should be discouraged. Parents can help their children to understand that television commercials intend to sell a product. Children can learn that their parents will help them by responsibly choosing healthy foods.

As obesity is determined by complex multifactorial conditions, prevention will take efforts at multiple levels of social organization. One example, EPODE (Ensemble Prévenons l’Obésité Des Enfants), is a multilevel prevention strategy, which began in France and has been adopted by more than 500 communities in 6 countries. The goal is for local environments, daycare centers, schools, recreational settings and families to adopt practices that promote healthy lifestyles for children from birth to 12 yr old. This initiative relies on 4 necessary components: political commitment to change, resources to support social marketing and changes, support services, evidence-based practices. All EPODE sites include monitoring and evaluation. Similar efforts are taking place in the United States. An example of a U.S. community effort is Shape Up Somerville, a citywide campaign to increase daily physical activity and healthy eating in Somerville, MA, which has been ongoing since 2002. This system’s intervention focuses on school health curricula, healthier food in schools and restaurants, safe routes to school, walkable and bikeable streets and worksite wellness. Communitywide programs are important because neighborhood environmental factors (poverty) have been associated with obesity in its residents. Although these efforts have resulted in lower weight gain in older children and adolescents, there is considerable interest in focusing earlier in the life cycle. Beginning obesity prevention during pregnancy and engaging health systems, early childhood programs, and community systems to support healthier life cycles is an approach with tremendous promise.

Bibliography is available at Expert Consult.
Table 47-6  Proposed Suggestions for Preventing Obesity

PREGNANCY
Normalize body mass index before pregnancy.
Do not smoke.
Maintain moderate exercise as tolerated.
In gestational diabetics, provide meticulous glucose control.
Gestational weight gain within the Institute of Medicine (IOM) recommendations.

POSTPARTUM AND INFANCY
Breastfeeding: exclusive for 4-6 mo, continue with other foods for 12 mo.
Postpone the introduction of baby foods to 4-6 mo and juices to 12 mo.

FAMILIES
Eat meals as a family in a fixed place and time.
Do not skip meals, especially breakfast.
No television during meals.
Use small plates, and keep serving dishes away from the table.
Avoid unnecessary sweet or fatty foods and sugar-sweetened drinks.
Remove televisions from children’s bedrooms; restrict times for television viewing and video games.
Do not use food as a reward.

SCHOOLS
Eliminate candy and cookie sales as fundraisers.
Review the contents of vending machines and replace with healthier choices; eliminate sodas.
Avoid financial support for sports teams from beverage and food industries.
Install water fountains and hydration stations.
Educate teachers, especially physical education and science faculty, about basic nutrition and the benefits of physical activity.
Educate children from preschool through high school on appropriate diet and lifestyle.
Mandate minimum standards for physical education, including 60 min of strenuous exercise 5 times weekly.
Encourage “the walking school bus”: groups of children walking to school with adult supervision.

COMMUNITIES
Increase family-friendly exercise and safe play facilities for children of all ages.
Develop more mixed residential-commercial developments for walkable and bicyclable communities.
Discourage the use of elevators and moving walkways.
Provide information on how to shop and prepare healthier versions of culture-specific foods.

HEALTHCARE PROVIDERS
Explain the biologic and genetic contributions to obesity.
Give age-appropriate expectations for body weight in children.
Work toward classifying obesity as a disease to promote recognition, reimbursement for care, and willingness and ability to provide treatment.

INDUSTRY
Mandate age-appropriate nutrition labeling for products aimed at children (e.g., red light/green light foods, with portion sizes).
Encourage marketing of interactive video games in which children must exercise in order to play.
Use celebrity advertising directed at children for healthful foods to promote breakfast and regular meals.
Reduce portion size (drinks and meals).

GOVERNMENT AND REGULATORY AGENCIES
Classify childhood obesity as a legitimate disease.
Find novel ways to fund healthy lifestyle programs (e.g., with revenues from food and drink taxes).
Subsidize government-sponsored programs to promote the consumption of fresh fruits and vegetables.
Provide financial incentives to industry to develop more healthful products and to educate the consumer on product content.
Provide financial incentives to schools that initiate innovative physical activity and nutrition programs.
Allow tax deductions for the cost of weight loss and exercise programs.
Provide urban planners with funding to establish bicycle, jogging, and walking paths.
Ban advertising of fast foods, nonnutritious foods, and sugar-sweetened beverages directed at preschool children, and restrict advertising to school-age children.
Ban toys as gifts to children for purchasing fast foods.


Table 47-7  Anticipatory Guidance: Establishing Healthy Eating Habits in Children

Do not punish a child during mealtimes with regard to eating. The emotional atmosphere of a meal is very important. Interactions during meals should be pleasant and happy.
Do not use foods as rewards.
Parents, siblings, and peers should model healthy eating, tasting new foods, and eating a well-balanced meal.
Children should be exposed to a wide range of foods, tastes, and textures.
New foods should be offered multiple times. Repeated exposure leads to acceptance and liking.
Forcing a child to eat a certain food will decrease the child’s preference for that food. Children’s wariness of new foods is normal and should be expected. Offering a variety of foods with low-energy density helps children balance energy intake.
Parents should control what foods are in the home. Restricting access to foods in the home will increase rather than decrease a child’s desire for that food.
Children tend to be more aware of satiety than adults, so allow children to respond to satiety, and stop eating. Do not force children to “clean their plate.”

Bibliography


Chapter 47  Overweight and Obesity


OVERVIEW OF VITAMIN A
Vitamin A is a fat-soluble micronutrient that cannot be synthesized de novo by the mammalian body, thus it is an obligatory dietary factor. The term vitamin A is generally used to refer to a group of compounds that possess the biologic activity of all-trans retinol (Fig. 48-1). As a fat-soluble micronutrient, vitamin A is recognized as being essential for all vertebrates for normal vision, reproduction, cell and tissue differentiation, and functions of the immune system. Vitamin A plays critical roles in neonatal development. It is required for normal embryonic development, hematopoiesis, immune response, metabolism, and growth and differentiation of many types of cells.

Vitamin A can be obtained from the diet where its main form is as retinyl esters, such as retinyl palmitate, which are called preformed vitamin A. They are found primarily in certain foods of animal origin. Organ meats (especially liver, kidney) are very rich in vitamin A, while other meats, milk, and cheese contain moderate levels. Other sources of vitamin A include several provitamin A carotenoids, which are found naturally in many fruits and vegetables (pumpkin, squash, sweet potato), and leafy green vegetables (chard, spinach, broccoli). One of the most abundant carotenoids is β-carotene. α-Carotene and β-cryptoxanthin also possess vitamin A activity at a lower bioactivity. In the body, these precursors are used for the synthesis of 2 essential metabolites of vitamin A. One is all-trans retinoic acid, the form of vitamin A required for cell differentiation and the regulation of gene transcription. It is the most bioactive form of vitamin A. The other is 11-cis retinal, required for vision. It functions as the light-absorbing chromophore of the visual pigments rhodopsin and iodopsin.

Figure 48-1 Vitamin A structures (A) and overview of vitamin A metabolism (B).

METABOLISM OF VITAMIN A
Ingested retinyl esters must first be hydrolyzed in the intestinal lumen, a process that liberates unesterified retinol, for the absorption of vitamin A. Most of the retinol is then reesterified in the enterocytes. The absorption of preformed vitamin A is very efficient. Approximately 70-90% of dietary preformed vitamin A is absorbed as long as there is ~10 g or more fat in the meal. Chronic intestinal disorders or lipid malabsorption can result in vitamin A deficiency. Uncleaved provitamin-A carotenoids in the intestine are also incorporated into chylomicrons and delivered to various tissues. The estimated absorption efficiency of carotenoids is approximately 20-50%, and appears to be more variable among individuals than for preformed vitamin A. The efficiency of conversion of B-carotene to retinol is much lower than expected. The carotene cleavage enzyme β-carotene monooxygenase, present in the enterocyte, exhibits certain single nucleotide polymorphisms that reduce the efficiency of conversion of β-carotene to retinol.

Once retinol is esterified in the enterocyte, retinyl ester is then packaged into nascent chylomicrons, which are then secreted into the lymphatic vessels and transported via the circulation to the liver or to other tissues. When vitamin A status is adequate, most mammals, including humans, store most of their total body vitamin A in the liver, within stellate cells. When their vitamin A status is deficient, vitamin A stores can be mobilized; the released retinol can be used by extrahepatic tissues. Stored vitamin A is released from the liver into the circulation as retinol bound to its specific transport protein, retinol-binding protein (RBP), which binds to the thyroid hormone transport protein, transthyretin (TTR); this complex delivers retinol (as well as the thyroid hormone) to a large number of vitamin A target tissues. The major physiologic mediator of retinol uptake by cells in many tissues is Stra6, a widely expressed multitransmembrane domain protein that functions as a cell-surface receptor for retinol bound to RBP.

In target tissues, retinol is either esterified into retinyl esters for storage or oxidized into retinoic acid for function. In the eye, 11-cis-retinal is formed.

Vitamin A Status in Neonates
Neonates begin life with low levels of vitamin A, in plasma, liver, and extrahepatic tissues, compared with those in adults. Normal plasma levels of retinol are 20-50 µg/dL in infants, and increase gradually as children become older. Median serum retinol values are 1.19 µmol/L in both boys and girls ages 4-8 yr; 1.4 and 1.33 µmol/L in boys and...
Inflammation as a Cause of Low Plasma Retinol

Inflammation is a cause of reduced levels of plasma retinol as a result of reduced synthesis of RBP and TTR. This condition may mimic a lack of vitamin A, but will not be corrected by supplementation. In U.S. adults, those with moderately elevated levels of C-reactive protein, indicative of mild inflammation, had lower average plasma retinol levels. The extent to which inflammation is a factor in low plasma retinol in children is uncertain but it is likely to be significant in acute infectious diseases such as measles, and possibly in chronic inflammatory conditions such as cystic fibrosis.

FUNCTIONS OF VITAMIN A AND MECHANISMS OF ACTION

Except for its role in vision, the pleiotropic actions of this micronutrient include many systemic functions that are mediated at the gene level by all-trans-retinoic acid (RA), which is a ligand for specific nuclear transcription factors, the retinoid receptors: RARs and RXRs. When an RAR is activated by the presence of RA, it combines with an RXR, and the resulting heterodimer binds to specific DNA sequences present in retinoid responsive genes (RAREs and RXREs, respectively) and therefore induce or repress the expression of a large number of genes. In this manner, vitamin A, via its active form, RA, regulates many genes that are involved in the fundamental biologic activities of cells, such as cell division, cell death, and cell differentiation. The term retinoids includes both natural and synthetic compounds with vitamin A activity and is most often used in the context of vitamin A action at the gene level. A large number of synthetic retinoids have been produced and some have gained clinical acceptance, such as in the treatment of skin disorders and certain cancers.

Retinoic acid is among the most important signaling molecules in vertebrate ontogenesis. It affects many physiologic processes, including reproduction, growth, embryonic and fetal development, and bone development, in addition to respiratory, gastrointestinal, hematopoietic, and immune functions. The role of vitamin A in immune function and host defense is particularly important in developing countries, where vitamin A supplementation or therapy reduces the morbidity and mortality rates of various diseases, such as measles (see Chapter 246).

Vitamin A plays a critical nongenomic role in vision. The human retina has 2 distinct photoreceptor systems: the rods, containing rhodopsin, which can detect low-intensity light, and the cones, containing iodopsin, which can detect different colors. The aldehyde form of vitamin A, retinal, is the prosthetic group on both visual proteins. The mechanism of vitamin A action in vision is based on the ability of the vitamin A molecule to photoisomerize (change shape when exposed to light). Thus, in the dark, low-intensity light isomerizes the rhodopsin prosthetic group, 11-cis retinal, to all-trans-retinal, generating an electrical signal that is transmitted via the optic nerve to the brain and results in visual sensation.

VITAMIN A DEFICIENCY

If the growing child has a well-balanced diet and obtains vitamin A from foods that are rich in vitamin A or provitamin-A (Table 48-1), the risk of vitamin A deficiency is small. However, even subclinical vitamin A deficiency can have serious consequences.

Deficiency states in developed countries are rare, except in some impoverished populations (see Chapter 46) or after mistakes in food preparation or with fad diets, but they are common in many developing countries and are often associated with global malnutrition (see Chapter 46). In the clinical setting, vitamin deficiencies can also occur as complications in children with various chronic disorders or diseases. Information obtained in the medical history related to dietary habits can be important in identifying the possibility of such nutritional problems. Except for vitamin A, toxicity from excess intake of vitamins is rare. Table 48-1 summarizes the food sources, functions, and deficiency and excess symptoms of the vitamins.

Clinical Manifestations of Vitamin A Deficiency

The most obvious symptoms of vitamin A deficiency are associated with the requirement of this vitamin for the maintenance of epithelial functions. In the intestines, a normal mucus-secreting epithelium (normal goblet cell function) is an effective barrier against pathogens that can cause diarrhea. Similarly, in the respiratory tract, a mucus-secreting epithelium is essential for the disposal of inhaled pathogens and toxicants. Characteristic changes as a result of vitamin A deficiency in the epithelia include a proliferation of basal cells, hyperkeratosis, and

Table 48-1: Vitamin A Characteristics

<table>
<thead>
<tr>
<th>NAMES AND SYNONYMS</th>
<th>CHARACTERISTICS</th>
<th>BIOCHEMICAL ACTION</th>
<th>EFFECTS OF DEFICIENCY</th>
<th>EFFECTS OF EXCESS</th>
<th>SOURCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinol (vitamin A₁); 1 µg retinol = 3.3 IU vitamin A = 1 RAE</td>
<td>Fat-soluble; heat-stable; destroyed by oxidation, drying Bile necessary for absorption Stored in liver Protected by vitamin E</td>
<td>In vision, as retinal, for synthesis of the visual pigments rhodopsin and iodopsin In growth, reproduction, embryonic and fetal development, bone growth, immune and epithelial functions, via retinoic acid as a ligand for specific nuclear transcription factors, regulating genes involved in many fundamental cellular processes</td>
<td>Nyctalopia Photophobia, xerophthalmia, Bitot spots, conjunctivitis, keratomalacia leading to blindness Faulty epiphyseal bone formation Defective tooth enamel Keratinization of mucous membranes and skin Retarded growth Impaired resistance to infection, anemia, reproductive failure, fetal abnormalities</td>
<td>Anorexia, slow growth, drying and cracking of skin, enlargement of liver and spleen, swelling and pain of long bones, bone fragility, increased intracranial pressure, alopecia, carotenemia Fetal abnormalities</td>
<td>Liver, fish liver oils Dairy products, except skim milk Egg yolk, fortified margarine, fortified skim milk Carotenoids from plants: green vegetables, yellow fruits, and vegetables</td>
</tr>
<tr>
<td>Provitamins A: the plant pigments α-, β-, and γ-carotenes and cryptoxanthin have partial retinol activity: 12 µg β-carotene, or 24 µg other provitamin A carotenoids = 1 µg retinol</td>
<td>In vision, as retinal, for synthesis of the visual pigments rhodopsin and iodopsin In growth, reproduction, embryonic and fetal development, bone growth, immune and epithelial functions, via retinoic acid as a ligand for specific nuclear transcription factors, regulating genes involved in many fundamental cellular processes</td>
<td>Nyctalopia Photophobia, xerophthalmia, Bitot spots, conjunctivitis, keratomalacia leading to blindness Faulty epiphyseal bone formation Defective tooth enamel Keratinization of mucous membranes and skin Retarded growth Impaired resistance to infection, anemia, reproductive failure, fetal abnormalities</td>
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<td>Liver, fish liver oils Dairy products, except skim milk Egg yolk, fortified margarine, fortified skim milk Carotenoids from plants: green vegetables, yellow fruits, and vegetables</td>
<td></td>
</tr>
</tbody>
</table>

RAE, retinol activity equivalent.
formation of stratified cornified squamous epithelium. Squamous metaplasia of the renal pelvis, ureters, vaginal epithelium, and the pancreatic and salivary ducts can lead to increased infections in these areas. In the urinary bladder, loss of epithelial integrity can result in pyuria and hematuria. Epithelial changes in the skin caused by vitamin A deficiency are manifested as dry, scaly, hyperkeratotic patches, commonly on the arms, legs, shoulders, and buttocks. The combination of defective epithelial barriers to infection, low immune response, and lowered response to inflammatory stress, all because of insufficient vitamin A, can cause poor growth and serious health problems in children.

The most characteristic and specific signs of vitamin A deficiency are eye lesions, but they may be manifest rather late in the progression of vitamin A deficiency. Lesions caused by vitamin A deficiency develop insidiously and rarely occur before 2 yr of age. An early symptom is delayed adaptation to the dark, a result of reduced resynthesis of rhodopsin; later, when vitamin A deficiency is more advanced, it leads to night blindness as a consequence of the absence of retinal in the visual pigment, rhodopsin, of the retina. Photophobia is a common symptom. The pigment epithelium, the structural element of the retina, keratinizes. When the pigment epithelium degenerates, the rods and cones have no support and eventually break down, resulting in blindness.

As vitamin A deficiency progresses, the corneal and conjunctival epithelial tissues of the eye become severely altered; this change results from a lack of sufficient RA for normal epithelial cell morphology and function. The cornea protects the eye from the environment and is also important in light refraction. In early vitamin A deficiency, the cornea keratinizes, becomes opaque, is susceptible to infection, and forms dry, scaly layers of cells (xerophthalmia). The conjunctiva keratinizes and develops plaques (Bitot spots [Fig. 48-2]). In later stages, infection occurs, lymphocytes infiltrate, and the cornea becomes wrinkled; it degenerates irreversibly (keratomalacia and corneal ulceration), resulting in blindness. Advanced xerophthalmia (Fig. 48-3) and xerophthalmia with permanent damage to the eye (Fig. 48-4) may develop if untreated. These eye lesions are primarily diseases of the young and are a major cause of blindness in developing countries. Although rates of xerophthalmia have fallen, the number of affected children is still too high.

Other clinical signs of vitamin A deficiency include poor overall growth, diarrhea, susceptibility to infections, anemia, apathy, mental retardation, and increased intracranial pressure, with wide separation of the cranial bones at the sutures. There may be vision problems as a consequence of bone overgrowth causing pressure on the optic nerve.

Malnutrition, particularly protein deficiency, can cause vitamin A deficiency by the impaired synthesis of retinol transport protein. In developing countries, subclinical or clinical zinc deficiency can increase the risk of vitamin A deficiency. There is also some evidence of marginal zinc intakes in children in the United States.

**Diagnosis**

Dark adaptation tests can be used to assess early-stage vitamin A deficiency. Although Bitot spots develop relatively early, those related to active vitamin A deficiency are usually confined to preschool-age children. Xerophthalmia is a very characteristic lesion of vitamin A deficiency. Caution must be exercised to exclude other, similar eye abnormalities from those associated with vitamin A deficiency. There are 3 useful indicators for detecting marginal vitamin A status, although they are mostly limited to research settings: conjunctival impression cytology, relative dose response, and modified relative dose response. A diet history can also be useful in suggesting or ruling out low intake as a cause. There is a relatively high prevalence of marginal vitamin A status among pregnant and lactating women. The plasma retinol level is not an accurate indicator of vitamin A status unless the deficiency is severe and liver stores are depleted, in which case low plasma retinol is likely to be evident. In children, plasma retinol values of <0.35 µmol/L are considered to be very deficient, 0.35-0.7 µmol/L are considered to be deficient, 0.7-1.05 µmol/L are considered to be marginal, and >1.05 µmol/L are considered to be adequate. It has long been thought that the liver vitamin A concentration must be 20 µg/g or higher to support a normal rate of secretion of retinol-RBP into plasma.

**Epidemiology and Public Health Issues**

Vitamin A deficiency and xerophthalmia still occur throughout much of the developing world and are linked to undernourishment and complicated by illness. Programs to provide periodic large doses of vitamin A have been instituted in many low-income countries in which vitamin

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*Figure 48-2* Bitot spots with hyperpigmentation seen in a 10 mo old Indonesian boy. *(From Oomen HAPC: Vitamin A deficiency, xerophthalmia and blindness, Nutr Rev 6:161–166, 1974.)*

*Figure 48-3* Advanced xerophthalmia with an opaque, dull cornea and some damage to the iris in a 1 yr old boy. *(From Oomen HAPC: Vitamin A deficiency, xerophthalmia and blindness, Nutr Rev 6:161–166, 1974.)*

*Figure 48-4* Recovery from xerophthalmia, showing a permanent eye lesion. *(From Bloch CE: Blindness and other disease arising from deficient nutrition [lack of fat soluble A factor], Am J Dis Child 27:139, 1924.)*
A deficiency is still a public health problem. Vitamin A supplementation is considered part of the strategy of the World Health Organization’s Millennium Development Goals to reduce <5 yr mortality. Other strategies being tested include improving the content of β-carotene in staple foods through plant breeding (biofortification).

### Dietary Reference Intakes for the Healthy Population

Table 48-2 summarizes the dietary reference intakes for infants and children. Dietary reference intake values include the estimated average requirement, which is the mean biologic requirement for the nutrient in the population; the recommended dietary allowance (RDA), which is set to cover the needs of >97% of the population (thus the needs of many people are more than covered by the RDA); and the upper level (UL), an intake level above which risk of adverse effects may increase; the UL pertains only to chronic consumption of preformed vitamin A.

The RDA is expressed as retinol activity equivalents (RAEs; 1 RAE = 1 µg all-trans-retinol; equivalents for provitamin-A in foods = 12 µg β-carotene, 24 µg α-carotene, or 24 µg β-cryptoxanthin). From infancy to age 18 yr, the RDA increases as a consequence of increased body size, becoming higher for boys than girls during adolescence. During pregnancy, the RDA is 750-770 µg, and during lactation, the RDA is increased to 1,200-1,300 µg to ensure sufficient vitamin A content during breastfeeding.

It is noteworthy that, especially for young children, the UL is not far above the RDA, differing by only 2-fold in some age groups. This suggests that for children whose diet is good, care should be taken not to overuse dietary supplements containing preformed vitamin A and/or to avoid excessive consumption of foods that are rich in vitamin A, such as liver.

### Vitamin A for Treatment of Deficiency

The safety and efficacy of vitamin A supplementation depend on the patient’s state of health and the regimen of other treatments. A daily supplement of 1,500 µg of vitamin A is sufficient for treating latent vitamin A deficiency, after which intake an at RDA level should be the goal. In children without overt vitamin A deficiency, morbidity and mortality rates from viral infections, such as measles, have been reduced by administration of weekly doses equivalent to the RDA level of vitamin A, or higher doses of 30-60 mg of retinol (100,000-200,000 IU) given once or twice, under careful monitoring to avoid toxicity associated with excess vitamin A. Xerophthalmia is treated by giving 1,500 µg/kg body weight orally for 5 days followed by intramuscular injection of 7,500 µg of vitamin A in oil, until recovery.

Vitamin A is also used in preterm infants for improvement of respiratory function and prevention of the development of chronic lung disease. An analysis of 9 randomized controlled trials of vitamin A found that vitamin A appears to be beneficial in reducing death or oxygen requirement with no differences in neurodevelopmental outcomes.

### HYPERVITAMINOSIS A

Chronic hypervitaminosis A results from excessive ingestion of preformed vitamin A (retinol or retinyl ester), generally for several weeks or months. The cause is often excessive use of vitamin A-containing supplements, or food faddism resulting in excessive intakes of organ meats. Toxicity can be induced in adults and children with chronic daily intakes of 15,000 µg and 6,000 µg, respectively. As there is no antidote for hypervitaminosis A, the prevention of this condition is most important. Symptoms may subside rapidly on withdrawal of the vitamin, but the rate of improvement depends on the amount of vitamin A that has built up in tissues. In extreme cases, hypervitaminosis A can be fatal. Signs of subacute or chronic toxicity can include headache; vomiting; anorexia; dry, itchy desquamating skin; seborrheic cutaneous lesions; fissuring at the corners of the mouth; alopecia and/or coarsening of the hair; bone abnormalities; swelling of the bones; enlargement of the liver and spleen; diplopia; increased intracranial pressure; irritability; stupor; limited motion; and dryness of the mucous membranes; desquamation of the palms and the soles of the feet. Radiographs may show hyperostosis affecting several long bones, especially in the middle of the shafts (Fig. 48-5). Serum levels of vitamin

![Figure 48-5](image_url)
A are elevated, mostly as retinyl ester contained in lipoproteins, which may contribute to membrane damage and symptoms, including release of liver enzymes into plasma. Hypercalcemia and/or liver cirrhosis may be present. Hypervitaminosis A is distinct from cortical hyperostosis (see Chapter 700).

In young children, toxicity is associated with vomiting and bulging fontanels. An affected child has anorexia, pruritus, and a lack of weight gain. Acute hypervitaminosis A, such as after consumption of a single large (30-60 mg dose) of vitamin A may include nausea, vomiting, and drowsiness; less-common symptoms include diplopia, papilledema, cranial nerve palsies, and other symptoms suggesting pseudotumor cerebri.

A syndrome of severe congenital malformations may occur in infants of mothers who have consumed therapeutic doses (0.5-1.5 mg/kg) of oral 13-cis-retinoic acid (e.g., Accutane), generally taken for the treatment of acne or cancer, during the 1st trimester of pregnancy. These malformations result in a high incidence (>20%) of spontaneous abortions and birth defects including characteristic craniofacial abnormalities. The U.S. Food and Drug Administration has increased the stringency of prescription of such drugs in women of childbearing age to attempt to reduce these birth defects.

Excessive intake of carotenoids is not associated with toxicity but can cause yellow coloration of the skin (carotenodermia) and serum (carotenemia) that disappears when intake is reduced. Children with liver disease, diabetes mellitus, or hypothyroidism are more susceptible. Food faddism including an excessive consumption of carotene-rich foods may be a cause of this condition.

Bibliography is available at Expert Consult.
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Bibliography
Vitamin B complex includes a number of water-soluble nutrients, including thiamine (B₁), riboflavin (B₂), niacin (B₃), pyridoxine (B₆), folate, cobalamin (B₁₂), biotin, and pantothenic acid. Choline and inositol are also considered part of the B complex and are important for normal body functions, but specific deficiency syndromes have not been attributed to a lack of these factors in the diet.

B-complex vitamins serve as coenzymes in many metabolic pathways that are functionally closely related. Consequently, a lack of one of the vitamins has the potential to interrupt a chain of chemical processes, including reactions that are dependent on other vitamins, and ultimately can produce diverse clinical manifestations. Because diets deficient in any one of the B-complex vitamins are often poor sources of other B vitamins, manifestations of several vitamin B deficiencies usually can be observed in the same person. It is therefore a general practice in a patient who has evidence of deficiency of a specific B vitamin to treat with the entire B-complex group of vitamins.

**49.1 Thiamine (Vitamin B₁)**

H.P.S. Sachdev and Dheeraj Shah

Thiamine diphosphate, the active form of thiamine, serves as a cofactor for several enzymes involved in carbohydrate catabolism such as pyruvate dehydrogenase, transketolase, and α-ketoglutarate. These enzymes also play a role in the hexose monophosphate shunt that generates nicotinamide adenine dinucleotide phosphate (NADP) and pentose for nucleic acid synthesis. Thiamine is also required for the synthesis of acetylcholine and γ-aminobutyric acid, which have important roles in nerve conduction. Thiamine is absorbed efficiently in the gastrointestinal (GI) tract, and may be deficient in persons with GI or liver disease. The requirement of thiamine is increased when carbohydrates are taken in large amounts and during periods of increased metabolism, such as fever, muscular activity, hyperthyroidism, pregnancy, and lactation. Alcohol affects various aspects of thiamine transport and uptake, contributing to the deficiency in alcoholics.

Pork (especially lean), fish, and poultry are good nonvegetarian dietary sources of thiamine. Main sources of thiamine for vegetarians are rice, oat, wheat, and legumes. Most ready-to-eat breakfast cereals are enriched with thiamine. Thiamine is water soluble and heat labile; most of the vitamin is lost when the rice is repeatedly washed and the cooking water is discarded. The breast milk of a well-nourished mother provides adequate thiamine; breastfed infants of thiamine-deficient mothers are at risk for deficiency. Thiamine antagonists (coffee, tea) and thiaminases (fermented fish) may contribute to thiamine deficiency. Most infants and older children consuming a balanced diet obtain an adequate intake of thiamine from food and do not require supplements.

**DEFICIENCY**

Deficiency of thiamine is associated with severely malnourished states, including malignancy and following surgery. The disorder (or spectrum of disorders) is classically associated with a diet consisting largely of polished rice (oriental beriberi); it can also arise if highly refined wheat flour forms a major part of the diet, in alcoholics, and in food faddists (occidental beriberi). Thiamine deficiency has often been reported from inhabitants of refugee camps consuming the polished rice–based monotonous diets. Low thiamine concentrations are also noted during critical illnesses.

Thiamine-responsive megaloblastic anemia (TRMA) syndrome is a rare autosomal recessive disorder characterized by megaloblastic anemia, diabetes mellitus, and sensorineural hearing loss, responding in varying degrees to thiamine treatment. The syndrome occurs because of mutations in the SLC19A2 gene, encoding a thiamine transporter protein, leading to abnormal thiamine transportation and cellular vitamin deficiency. Thiamine and related vitamins may improve the outcome in children with Leigh encephalomyelopathy and type 1 diabetes mellitus.

**Clinical Manifestations**

Thiamine deficiency can develop within 2-3 mo of a deficient intake. Early symptoms of thiamine deficiency are nonspecific, such as fatigue, apathy, irritability, depression, drowsiness, poor mental concentration, anorexia, nausea, and abdominal discomfort. As the condition progresses, more-specific manifestations of beriberi, such as peripheral neuritis (manifesting as tingling, burning, paresthesias of the toes and feet), decreased deep tendon reflexes, loss of vibration sense, tenderness and cramping of the leg muscles, heart failure, and psychological disturbances, develop. Patients can have ptosis of the eyelids and atrophy of the optic nerve. Hoarseness or aphonia caused by paralysis of the laryngeal nerve is a characteristic sign. Muscle atrophy and tenderness of the nerve trunks are followed by ataxia, loss of coordination, and loss of deep sensation. Later signs include increased intracranial pressure, meningismus, and coma. The clinical picture of thiamine deficiency is usually divided into a dry (neuritic) type and a wet (cardiac) type. The disease is wet or dry depending on the amount of fluid that accumulates in the body as a result of factors such as cardiac and renal dysfunction, even though the exact cause for this edema is unknown. Many cases of thiamine deficiency show a mixture of both features and are more properly termed thiamine deficiency with cardiopathy and peripheral neuropathy.

The classic clinical triad of Wernicke encephalopathy (mental status changes, ocular signs, ataxia) is rarely reported in infants and
young children with severe deficiency secondary to malignancies or feeding of defective formula. An epidemic of life-threatening thiamine deficiency was seen in infants fed a defective soy-based formula that had undetectable thiamine levels. Manifestations included emesis, lethargy, restlessness, ophthalmoplegia, abdominal distention, developmental delay, failure to thrive, lactic acidosis, nystagmus, diarrhea, apnea, seizures, and auditory neuropathy.

Death from thiamine deficiency usually is secondary to cardiac involvement. The initial signs are cyanosis and dyspnea, but tachycardia, enlargement of the liver, loss of consciousness, and convulsions can develop rapidly. The heart, especially the right side, is enlarged. The electrocardiogram shows an increased Q-T interval, inverted T waves, and low voltage. These changes, as well as the cardiomegaly, rapidly revert to normal with treatment, but without prompt treatment, cardiac failure can develop rapidly and result in death. In fatal cases of beriberi, lesions are principally located in the heart, peripheral nerves, subcutaneous tissue, and serous cavities. The heart is dilated, and fatty degeneration of the myocardium is common. Generalized edema or edema of the legs, serous effusions, and venous engorgement are often present. Degeneration of myelin and axon cylinders of the peripheral nerves, with wallerian degeneration beginning in the distal locations, is also common, particularly in the lower extremities. Lesions in the brain include vascular dilation and hemorrhage.

**Diagnosis**

The diagnosis is often suspected on the basis of clinical setting and compatible symptoms. A high index of suspicion in children presenting with unexplained cardiac failure may sometimes be lifesaving. Objective biochemical tests of thiamine status include measurement of erythrocyte transketolase activity and the thiamine pyrophosphate effect. The biochemical diagnostic criteria of thiamine deficiency consist of low erythrocyte transketolase activity and high thiamine pyrophosphate effect (normal range: 0-14%). Urinary excretion of thiamine or its metabolites (thiazole or pyrimidine) after an oral loading dose of thiamine may also be measured to help identify the deficiency state. MRI changes of thiamine deficiency in infants are characterized by bilateral symmetric hyperintensities of the basal ganglia and frontal lobe, in addition to the lesions in the mamillothalamic bodies, periaqueductal region, and thalami described in adults.

**Prevention**

A maternal diet containing sufficient amounts of thiamine prevents thiamine deficiency in breastfed infants, and infant formulas marketed in all developed countries provide recommended levels of intake. During complementary feeding, adequate thiamine intake can be achieved with a varied diet that includes meat and enriched or whole-grain cereals. When the staple cereal is polished rice, special efforts need to be made to include legumes and/or nuts in the ration. Thiamine and other vitamins can be retained in rice by parboiling, a process of steaming the rice in the husk before milling. Improvement in cooking techniques, such as not discarding the water used for cooking, minimal washing of grains, and reduction of cooking time helps to minimize the thiamine losses during the preparation of food. Thiamine supplementation should be ensured during total parenteral nutrition.

**Treatment**

In the absence of GI disturbances, oral administration of thiamine is effective. Children with cardiac failure, convulsions, or coma should be given 10 mg of thiamine intramuscularly or intravenously daily for the 1st wk. This treatment should then be followed by 3-5 mg of thiamine per day orally for at least 6 wk. The response is dramatic in infants and in those having predominantly cardiovascular manifestations, whereas the neurologic response is slow and often incomplete. Epilepsy, mental disability, and language and auditory problems of varying degree have been reported in survivors of severe infantile thiamine deficiency.

Patients with beriberi often have other B-complex vitamin deficiencies; therefore, all other B-complex vitamins should also be adminis-tered. Treatment of TRMA and other dependency states require higher dosages (100-200 mg/day). The anemia responds well to thiamine administration, and insulin for associated diabetes mellitus can also be discontinued in many cases of TRMA.

**TOXICITY**

There are no reports of adverse effects from consumption of excess thiamine by ingestion of food or supplements. A few isolated cases of pruritus and anaphylaxis have been reported in patients after parenteral administration of the vitamin.

Bibliography is available at Expert Consult.

### 49.2 Riboflavin (Vitamin B₂)

**H.P.S. Sachdev and Dheeraj Shah**

Riboflavin is part of the structure of the coenzymes flavin adenine dinucleotide (FAD) and flavin mononucleotide, which participate in oxidation-reduction reactions in numerous metabolic pathways and in energy production via the mitochondrial respiratory chain. Riboflavin is stable to heat, but is destroyed by light. Milk, eggs, organ meats, legumes, and mushrooms are rich dietary sources of riboflavin. Most commercial cereals, flours, and breads are enriched with riboflavin.

**DEFICIENCY**

The causes of riboflavin deficiency are mainly related to malnourished and malabsorptive states, including GI infections. Treatment with some drugs, such as probenecid, phenothiazine, or oral contraceptives, can also cause the deficiency. The side chain of the vitamin is photochemically destroyed during phototherapy for hyperbilirubinemia, as it is involved in the photosensitized oxidation of bilirubin to more polar excretable compounds. Isolated complex II deficiency, a rare mitochondrial disease manifesting in infancy and childhood, responds favorably to riboflavin supplementation and thus can be termed a dependency state. Brown-Vialetto-Van Laere syndrome (BVVLS), a rare neurologic disorder characterized by progressive neurologic deterioration, hypotonia, sensorineural hearing loss, and pontobulbar palsy responds to treatment with high doses of riboflavin. Mutations in genes coding for riboflavin transporter proteins have been identified in children with BVVLS.

**Clinical Manifestations**

Clinical features of riboflavin deficiency include cheilosis, glossitis, keratitis, conjunctivitis, photophobia, lacrimation, corneal vascularization, and seborrheic dermatitis. Cheilosis begins with pallor at the angles of the mouth and progresses to thinning and maceration of the epithelium, leading to fissures extending radially into the skin (Fig. 49-1). In glossitis, the tongue becomes smooth, with loss of papillary structure (Fig. 49-2). Normochromatic, normocytic anemia may also be seen because of the impaired erythropoiesis. A low riboflavin content of the maternal diet has been linked to congenital heart defects, but the evidence is weak.

**Diagnosis**

Most often, the diagnosis is based on the clinical features of angular cheilosis in a malnourished child, which responds promptly to riboflavin supplementation. A functional test of riboflavin status is done by measuring the activity of erythrocyte glutathione reductase (EGR), with and without the addition of FAD. An EGR activity coefficient (ratio of EGR activity with added FAD to EGR activity without FAD) of >1.4 is used as an indicator of deficiency. Urinary excretion of riboflavin <30 µg/24 hr also suggests low intakes.

**Prevention**

Table 49-1 lists the recommended daily allowance of riboflavin for infants, children, and adolescents. Adequate consumption of milk, milk products, and eggs prevents riboflavin deficiency. Fortification of

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**Table 49-1**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Riboflavin RDA (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>0.2-0.4</td>
</tr>
<tr>
<td>Toddlers</td>
<td>0.3-0.5</td>
</tr>
<tr>
<td>Children</td>
<td>0.5-0.6</td>
</tr>
<tr>
<td>Adolescents</td>
<td>0.6-0.7</td>
</tr>
</tbody>
</table>
**Bibliography**


Table 49-1: Water-Soluble Vitamins

<table>
<thead>
<tr>
<th>NAMES AND SYNONYMS</th>
<th>BIOCHEMICAL ACTION</th>
<th>EFFECTS OF DEFICIENCY</th>
<th>TREATMENT OF DEFICIENCY</th>
<th>CAUSES OF DEFICIENCY</th>
<th>DIETARY SOURCES</th>
<th>RDA* BY AGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiamine (vitamin B1)</td>
<td>Coenzyme in carbohydrate metabolism, Nucleic acid synthesis, Neurotransmitter synthesis</td>
<td>Neurologic (dry beriberi): irritability, peripheral neuritis, muscle tenderness, ataxia. Cardiac (wet beriberi): tachycardia, edema, cardiomegaly, cardiac failure.</td>
<td>3-5 mg/day PO thiamine for 6 wk</td>
<td>Polished rice-based diets, Malabsorptive states. Severe malnutrition, Malignancies, Alcoholism.</td>
<td>Meat, especially pork; fish; liver. Rice (unmilled), wheat germ; enriched cereals; legumes.</td>
<td>0-6 mo: 0.2 mg/day. 7-12 mo: 0.3 mg/day. 1-3 yr: 0.5 mg/day. 4-8 yr: 0.6 mg/day. 9-13 yr: 0.9 mg/day. 14-18 yr: Girls: 1.0 mg/day. Boys: 1.2 mg/day.</td>
</tr>
<tr>
<td>Riboflavin (vitamin B2)</td>
<td>Constituent of flavoprotein enzymes important in oxidation-reduction reactions: amino acid, fatty acid, and carbohydrate metabolism and cellular respiration.</td>
<td>Glossitis, photophobia, lacrimation, corneal vascularization, poor growth, cheilosis.</td>
<td>3-10 mg/day PO riboflavin</td>
<td>Severe malnutrition, Malabsorptive states. Prolonged treatment with phenothiazines, probenecid, or OCPs.</td>
<td>Milk, milk products, eggs, fortified cereals, green vegetables.</td>
<td>0-6 mo: 0.3 mg/day. 7-12 mo: 0.4 mg/day. 1-3 yr: 0.5 mg/day. 4-8 yr: 0.6 mg/day. 9-13 yr: 0.9 mg/day. 14-18 yr: Girls: 1.0 mg/day. Boys: 1.3 mg/day.</td>
</tr>
<tr>
<td>Niacin (vitamin B3)</td>
<td>Constituent of NAD and NADP, important in respiratory chain, fatty acid synthesis, cell differentiation, and DNA processing.</td>
<td>Pellagra manifesting as diarrhea, symmetric scaly dermatitis in sun-exposed areas, and neurologic symptoms of disorientation and delirium.</td>
<td>50-300 mg/day PO niacin</td>
<td>Predominantly maize-based diets. Anorexia nervosa, Carcinoid syndrome.</td>
<td>Meat, fish, poultry, Cereals, legumes, green vegetables.</td>
<td>0-6 mo: 0.2 mg/day. 7-12 mo: 0.4 mg/day. 1-3 yr: 6 mg/day. 4-8 yr: 8 mg/day. 9-13 yr: 12 mg/day. 14-18 yr: Girls: 14 mg/day. Boys: 16 mg/day.</td>
</tr>
<tr>
<td>Pyridoxine (vitamin B6)</td>
<td>Constituent of coenzymes for amino acid and glycogen metabolism, heme synthesis, steroid action, neurotransmitter synthesis.</td>
<td>Irritability, convulsions, hypochromic anemia. Failure to thrive, Oxaluria.</td>
<td>5-25 mg/day PO for deficiency states. 100 mg IM or IV for pyridoxine-dependent seizures.</td>
<td>Prolonged treatment with INH, penicillamine, OCPs.</td>
<td>Fortified ready-to-eat cereals, meat, fish, poultry, liver, bananas, rice, potatoes.</td>
<td>0-6 mo: 0.1 mg/day. 7-12 mo: 0.3 mg/day. 1-3 yr: 0.5 mg/day. 4-8 yr: 0.6 mg/day. 9-13 yr: 1.0 mg/day. 14-18 yr: Girls: 1.2 mg/day. Boys: 1.3 mg/day.</td>
</tr>
</tbody>
</table>

*Continued*
cereal products is helpful for those who follow vegan diets or who are consuming inadequate amounts of milk products for other reasons.

**Treatment**

Treatment includes oral administration of 3–10 mg/day of riboflavin, often as an ingredient of a vitamin B–complex mix. The child should also be given a well-balanced diet, including milk and milk products.

**TOXICITY**

No adverse effects associated with riboflavin intakes from food or supplements have been reported, and the upper safe limit for consumption has not been established. Although the photosensitizing property of this vitamin raises the possibility for some potential risks, limited absorption in high-intake situations precludes such concerns.

_Bibliography is available at Expert Consult._

### 49.3 Niacin (Vitamin B₃)

**H.P.S. Sachdev and Dheeraj Shah**

Niacin (nicotinamide or nicotinic acid) forms part of 2 cofactors, nicotinamide adenine dinucleotide and NADP, which are important in several biologic reactions, including the respiratory chain, fatty acid

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**Table 49-1  Water-Soluble Vitamins—cont’d**

<table>
<thead>
<tr>
<th>NAMES AND SYNTHONYS</th>
<th>BIOCHEMICAL ACTION</th>
<th>EFFECTS OF DEFICIENCY</th>
<th>TREATMENT OF DEFICIENCY</th>
<th>CAUSES OF DEFICIENCY</th>
<th>DIETARY SOURCES</th>
<th>RDA* BY AGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biotin</td>
<td>Cofactor for carboxylases, important in gluconeogenesis, fatty acid and amino acid metabolism</td>
<td>Scaly periorificial dermatitis, conjunctivitis, alopecia, lethargy, hypotonia, and withdrawn behavior</td>
<td>1-10 mg/day PO biotin</td>
<td>Consumption of raw eggs for prolonged periods</td>
<td>Liver, organ meats, fruits</td>
<td>0-6 mo: 5 µg/day 7-12 mo: 6 µg/day 1-3 yr: 8 µg/day 4-8 yr: 12 µg/day 9-13 yr: 20 µg/day 14-18 yr: 25 µg/day</td>
</tr>
<tr>
<td>Pantothenic acid (vitamin B₅)</td>
<td>Component of coenzyme A and acyl carrier protein involved in fatty acid metabolism</td>
<td>Experimentally produced deficiency in humans: irritability, fatigue, numbness, paresthesias (burning feet syndrome), muscle cramps</td>
<td>Isolated deficiency extremely rare in humans</td>
<td>Beef, organ meats, poultry, seafood, egg yolk Yeast, soybeans, mushrooms</td>
<td>0-6 mo: 1.7 mg/day 7-12 mo: 1.8 mg/day 1-3 yr: 2 mg/day 4-8 yr: 3 mg/day 9-13 yr: 4 mg/day 14-18 yr: 5 mg/day</td>
<td></td>
</tr>
<tr>
<td>Folic acid</td>
<td>Coenzymes in amino acid and nucleotide metabolism as an acceptor and donor of one-carbon units</td>
<td>Megaloblastic anemia Growth retardation, glossitis, Neural tube defects in progeny</td>
<td>0.5-1 mg/day PO folic acid</td>
<td>Malnutrition Malabsorptive states Malignancies Hemolytic anemias Anticonvulsant therapy</td>
<td>Enriched cereals, beans, leafy vegetables, citrus fruits, papaya</td>
<td>0-6 mo: 65 µg/day 7-12 mo: 80 µg/day 1-3 yr: 150 µg/day 4-8 yr: 200 µg/day 9-13 yr: 300 µg/day 14-18 yr: 400 µg/day</td>
</tr>
<tr>
<td>Cobalamin (vitamin B₁₂)</td>
<td>As deoxyadenosylcobalamin, acts as cofactor for lipid and carbohydrate metabolism As methylcobalamin, important for conversion of homocysteine to methionine and folic acid metabolism</td>
<td>Megaloblastic anemia, irritability, developmental delay, developmental regression, involuntary movements, hyperpigmentation</td>
<td>1,000 µg IM vitamin B₁₂</td>
<td>Vegan diets Malabsorptive states Crohn disease Intrinsic factor deficiency (pernicious anemia)</td>
<td>Organ meats, sea foods poultry, egg yolks, milk, fortified ready-to-eat cereals</td>
<td>0-6 mo: 0.4 µg/day 7-12 mo: 0.5 µg/day 1-3 yr: 0.9 µg/day 4-8 yr: 1.2 µg/day 9-13 yr: 1.8 µg/day 14-18 yr: 2.4 µg/day</td>
</tr>
<tr>
<td>Ascorbic acid (vitamin C)</td>
<td>Important for collagen synthesis, metabolism of cholesterol and neurotransmitters Antioxidant functions and nonheme iron absorption</td>
<td>Scurvy manifesting as irritability, tenderness and swelling of legs, bleeding gums, petechiae, ecchymoses, follicular hyperkeratosis, and poor wound healing</td>
<td>100-200 mg/day PO ascorbic acid for up to 3 mo</td>
<td>Predominantly milk-based (non–human milk) diets Severely malnutrition</td>
<td>Citrus fruits and fruit juices, peppers, berries, melons, tomatoes, cauliflower, leafy green vegetables</td>
<td>0-6 mo: 40 mg/day 7-12 mo: 50 mg/day 1-3 yr: 15 mg/day 4-8 yr: 25 mg/day 9-13 yr: 45 mg/day 14-18 yr: Girls: 65 mg/day Boys: 75 mg/day</td>
</tr>
</tbody>
</table>

*For healthy breastfed infants, the values represent adequate intakes, that is, the mean intake of apparently “normal” infants.

INH, isoniazid; NAD, nicotinamide adenine dinucleotide; NADP, nicotinamide adenine dinucleotide phosphate; OCP, oral contraceptive pill; RDA, recommended dietary allowance.

Bibliography
and steroid synthesis, cell differentiation, and DNA processing. Niacin is rapidly absorbed from the stomach and the intestines and can also be synthesized from tryptophan in the diet.

Major dietary sources of niacin are meat, fish, and poultry for non-vegetarians and cereals, legumes, and green leafy vegetables for vegetarians. Enriched and fortified cereal products and legumes also are major contributors to niacin intake. Milk and eggs contain little niacin but are good sources of tryptophan, which can be converted to nicotinamide adenine dinucleotide (60 mg tryptophan = 1 mg niacin).

DEFICIENCY

Pellagra, the classic niacin deficiency disease, occurs chiefly in populations where corn (maize), a poor source of tryptophan, is the major foodstuff. A severe dietary imbalance, such as in anorexia nervosa and in war or famine conditions, also can cause pellagra. Pellagra can also develop in conditions associated with disturbed tryptophan metabolism such as carcinoid syndrome and Hartnup disease.

Clinical Manifestations

The early symptoms of pellagra are vague: anorexia, lassitude, weakness, burning sensation, numbness, and dizziness. After a long period of deficiency, the classic triad of dermatitis, diarrhea, and dementia appears. Dermatitis, the most characteristic manifestation of pellagra, can develop suddenly or insidiously and may be initiated by irritants, including intense sunlight. The lesions first appear as symmetric areas of erythema on exposed surfaces, resembling sunburn, and might go unrecognized. The lesions are usually sharply demarcated from the surrounding healthy skin, and their distribution can change frequently. The lesions on the hands and feet often have the appearance of a glove or stocking (Fig. 49-3). Similar demarcations can also occur around the neck (Casal necklace) (Fig. 49-3). In some cases, vesicles and bullae develop (wet type). In others, there may be suppuration beneath the scaly, crusted epidermis; in still others, the swelling can disappear after a short time, followed by desquamation (Fig. 49-4). The healed parts of the skin might remain pigmented. The cutaneous lesions may be preceded by or accompanied by stomatitis, glossitis, vomiting, and/or diarrhea. Swelling and redness of the tip of the tongue and its lateral margins is often followed by intense redness, even ulceration, of the entire tongue and the papillae. Nervous symptoms include depression, disorientation, insomnia, and delirium.

The classic symptoms of pellagra usually are not well developed in infants and young children, but anorexia, irritability, anxiety, and apathy are common. Young patients might also have sore tongues and lips, and usually have dry and scaly skin. Diarrhea and constipation can alternate, and anemia can occur. Children who have pellagra often have evidence of other nutritional deficiency diseases.

Diagnosis

Because of lack of a good functional test to evaluate niacin status, the diagnosis of deficiency is usually made from the physical signs of glossitis, GI symptoms, and a symmetric dermatitis. Rapid clinical response to niacin is an important confirmatory test. A decrease in the concentration and/or a change in the proportion of the niacin metabolites N'-methyl-nicotinamide and 2-pyridone in the urine provide biochemical evidence of deficiency and can be seen before the appearance of overt signs of deficiency. Histopathologic changes from the affected skin include dilated blood vessels without significant inflammatory infiltrates, ballooning of the keratinocytes, hyperkeratosis, and epidermal necrosis.

Prevention

Adequate intakes of niacin are easily met by consumption of a diet that consists of a variety of foods and includes meat, eggs, milk, and enriched or fortified cereal products. The dietary reference intake (DRI) is expressed in mg niacin equivalents (NE) in which 1 mg NE = 1 mg niacin or 60 mg tryptophan. An intake of 2 mg of niacin is considered adequate for infants 0-6 mo of age; and 4 mg is adequate for infants 7-12 mo of age. For older children, the recommended...
intakes are 6 mg for 1-3 yr of age, 8 mg for 4-8 yr of age, 12 mg for 9-13 yr of age, and 14-16 mg for 14-18 yr of age.

**Treatment**

Children usually respond rapidly to treatment. A liberal and varied diet should be supplemented with 50-300 mg/day of niacin; in severe cases or in patients with poor intestinal absorption, 100 mg may be given intravenously. The diet should also be supplemented with other vitamins, especially other B-complex vitamins. Sun exposure should be avoided during the active phase of pellagra, and the skin lesions may be covered with soothing applications. Other coexisting nutrient deficiencies such as iron deficiency anemia should be treated. Even after successful treatment, the diet should continue to be monitored to prevent recurrence.

**TOXICITY**

There are no toxic effects associated with the intake of naturally occurring niacin in foods. Shortly after the ingestion of large doses of nictinic acid taken as a supplement or a pharmacologic agent, a person often experiences a burning, tingling, and itching sensation as well as flushing on the face, arms, and chest. Large doses of niacin also can have nonspecific GI effects and can cause cholestatic jaundice or hepatoxicity. Tolerable upper intake levels for children are approximately double the recommended dietary allowance.

*Bibliography is available at Expert Consult.*

### 49.4 Vitamin B₆ (Pyridoxine)

**H.P.S. Sachdev and Dheeraj Shah**

Vitamin B₆ includes a group of closely related compounds: pyridoxine, pyridoxal, pyridoxamine, and their phosphorylated derivatives. Pyridoxal 5’-phosphate (PLP) and, to a lesser extent, pyridoxamine phosphate function as coenzymes for many enzymes involved in amino acid metabolism, neurotransmitter synthesis, glycogen metabolism, and steroid action. If vitamin B₆ is lacking, glycine metabolism can lead to oxaluria. The major excretory product in the urine is 4-pyridoxic acid.

The vitamin B₆ content of human milk and infant formulas is adequate. Good food sources of the vitamin include fortified ready-to-eat cereals, meat, fish, poultry, liver, bananas, rice, and certain vegetables. Large losses of the vitamin can occur during high-temperature processing of foods or milling of cereals, whereas parboiling of rice prevents its loss.

**DEFICIENCY**

Because of the importance of vitamin B₆ in amino acid metabolism, high protein intakes can increase the requirement for the vitamin; the recommended daily allowances are sufficient to cover the expected range of protein intake in the population. The risk of deficiency is increased in persons taking medications that inhibit the activity of vitamin B₆ (isoniazid, penicillamine, corticosteroids, phenytoin, carbamazepine), in young women taking oral progesterone-estrogen contraceptives, and in patients receiving maintenance dialysis.

**Clinical Manifestations**

The deficiency symptoms seen in infants are listlessness, irritability, seizures, vomiting, and failure to thrive. Peripheral neuritis is a feature of deficiency in adults but is not usually seen in children. Electroencephalogram (EEG) abnormalities have been reported in infants as well as in young adult subjects in controlled depletion studies. Skin lesions include cheilosis, glossitis, and seborrheic dermatitis around the eyes, nose, and mouth. Microcytic anemia can occur in infants, but is not common. Oxaluria, oxalic acid bladder stones, hyperglycinemia, lymphopenia, decreased antibody formation, and infections also are associated with vitamin B₆ deficiency.

Several types of vitamin B₆ dependence syndromes, presumably resulting from errors in enzyme structure or function, respond to very large amounts of pyridoxine. These syndromes include pyridoxine-dependent epilepsy, a vitamin B₆–responsive anemia, xanthurenic aciduria, cystathioninuria, and homocystinuria (see Chapters 85, 456, and 601). Pyridoxine-dependent epilepsy involves mutations in the ALDH7A1 gene causing deficiency of antiquitin, an enzyme involved in dehydrogenation of 1-alpha-aminoadipic semialdehyde.

**Diagnosis**

The activity of the erythrocyte transaminases glutamic oxaloacetic transaminase and glutamic pyruvic transaminase is low in vitamin B₆ deficiency; tests measuring the activity of these enzymes before and after the addition of PLP may be useful as indicators of vitamin B₆ status. Abnormally high xanthurenic acid excretion after tryptophan ingestion also provides evidence of deficiency. Plasma PLP assays are being used more often, but factors other than deficiency can influence the results. Vitamin B₆ deficiency or dependence should be suspected in all infants with seizures. If more common causes of infantile seizures have been eliminated, 100 mg of pyridoxine can be injected, with EEG monitoring if possible. If the seizure stops, vitamin B₆ deficiency should be suspected. In older children, 100 mg of pyridoxine may be injected intramuscularly while the EEG is being recorded; a favorable response of the EEG suggests pyridoxine deficiency.

**Prevention**

Deficiency is unlikely in children consuming diets that meet their energy needs and contain a variety of foods. Parboiling of rice prevents the loss of vitamin B₆ from the grains. The DRIs for vitamin B₆ are 0.1 mg/day for infants up to 6 mo of age; 0.3 mg/day for ages 6 mo to 1 yr; 0.5 mg/day for ages 1-3 yr; 0.6 mg/day for ages 4-8 yr; 1.0 mg/day for ages 9-13 yr; and 1.2-1.3 mg/day for ages 14-18 yr. Infants whose mothers have received large doses of pyridoxine during pregnancy are at increased risk for seizures from pyridoxine dependence, and supplements during the 1st few weeks of life should be considered. Any child receiving a pyridoxine antagonist, such as isoniazid, should be carefully observed for neurologic manifestations; if these develop, vitamin B₆ should be administered or the dose of the antagonist should be decreased.

**Treatment**

Intramuscular or intravenous administration of 100 mg of pyridoxine is used to treat convulsions caused by vitamin B₆ deficiency. One dose should be sufficient if adequate dietary intake follows. For pyridoxine-dependent children, daily doses of 2-10 mg intramuscularly or 10-100 mg orally may be necessary.

**TOXICITY**

Adverse effects have not been associated with high intakes of vitamin B₆ from food sources. However, ataxia and sensory neuropathy have been reported with dosages as low as 100 mg/day in adults taking vitamin B₆ supplements for several months.

*Bibliography is available at Expert Consult.*

### 49.5 Biotin

**H.P.S. Sachdev and Dheeraj Shah**

Biotin functions as a cofactor for enzymes involved in carboxylation reactions within and outside mitochondria. These biotin-dependent carboxylases catalyze key reactions in gluconeogenesis, fatty acid metabolism, and amino acid catabolism. There is limited information on the biotin content of foods; it is believed to be widely distributed, thus making a deficiency unlikely. Avidin found in raw egg whites acts as a biotin antagonist. Signs of biotin deficiency have been demonstrated in persons who consume large amounts of raw egg whites over long periods. Deficiency also has been described in infants and children receiving enteral and parenteral
Bibliography


Bibliography


The adequate dietary intake values for biotin are 5 µg/day for ages 0-6 mo, 6 µg/day for ages 7-12 mo, 8 µg/day for ages 1-3 yr, 12 µg/day for ages 4-8 yr, 20 µg/day for ages 9-13 yr, and 25 µg/day for ages 14-18 yr. No toxic effects have been reported with very high doses.

Bibliography is available at Expert Consult.

49.6 Folate

H.P.S. Sachdev and Dheeraj Shah

Folate exists in a number of different chemical forms. Folic acid (pteroylglutamic acid) is the synthetic form used in fortified foods and supplements. Naturally occurring folates in foods retain the core chemical structure of pteroylglutamic acid but vary in their state of reduction, the single carbon moiety they bear, or the length of the glutamate chain. These polyglutamates are broken down and reduced in the small intestine to dihydro- and tetrahydrofolates, which are involved as coenzymes in amino acid and nucleotide metabolism as acceptors and donors of 1-carbon units. Folate is important for central nervous system development during embryogenesis.

Rice and cereals are rich dietary sources of folate, especially if enriched. Beans, leafy vegetables, and fruits such as oranges and papaya are good sources, too. The vitamin is readily absorbed from the small intestine and is broken down to monoglutamate derivatives by mucosal polyglutamate hydrolases. A high-affinity proton-coupled folate transporter (PCFT) seems to be essential for absorption of folate in intestine and in various cell types at low pH. The vitamin is also synthesized by the colonic bacteria, and the half-life of the vitamin is prolonged by enterohepatic recirculation.

DEFICIENCY

Because of its role in protein, DNA, and RNA synthesis, the risk of deficiency is increased during periods of rapid growth or increased cellular metabolism. Folate deficiency can result from poor nutrient content in diet, inadequate absorption (celiac disease, inflammatory bowel disease), increased requirement (sickle cell anemia, psoriasis, malignancies, periods of rapid growth as in infancy and adolescence), or inadequate utilization (long-term treatment with high-dose nonsteroidal antiinflammatory drugs; anticonvulsants such as phenytoin and phenobarbital; and methotrexate). Rare causes of deficiency are hereditary folate malabsorption, inborn errors of folate metabolism (methylene tetrahydrofolate reductase, methionine synthase reductase, and glutamate formiminotransferase deficiencies), and cerebral folate deficiency. A loss-of-function mutation in the gene coding for PCFT is the molecular basis for hereditary folate malabsorption. A high-affinity blocking autoantibody against the membrane-bound folate receptor in the choroid plexus preventing its transport across the blood–brain barrier is the likely cause of the infantile cerebral folate deficiency.

Clinical Manifestations

Folic acid deficiency results in megaloblastic anemia and hypersegmentation of neutrophils. Nonhematologic manifestations include glossitis, listlessness, and growth retardation not related to anemia. There is an association between low maternal folic acid status and neural tube defects, primarily spina bifida and anencephaly, and the role of periconceptional folic acid in their prevention is well established.

Hereditary folate malabsorption manifests at 1-3 mo of age with recurrent or chronic diarrhea, failure to thrive, oral ulcerations, neurologic deterioration, megaloblastic anemia, and opportunistic infections. Cerebral folate deficiency manifests at 4-6 mo of age with irritability, microcephaly, developmental delay, cerebellar ataxia, pyramidal tract signs, choreoathetosis, ballismus, seizures, and blindness as a result of optic atrophy. 5-Methyltetrahydrofolate levels are normal in serum and red blood cells (RBCs), but are markedly depressed in the cerebrospinal fluid.
Bibliography

Vitamin B<sub>12</sub>, in the form of deoxyadenosylcobalamin, functions as a cofactor for isomerization of methylmalonyl-CoA to succinyl-CoA, an essential reaction in lipid and carbohydrate metabolism. Methylcobalamin is another circulating form of vitamin B<sub>12</sub>, and is essential for methyl group transfer during the conversion of homocysteine to methionine. This reaction also requires a folic acid cofactor and is important for protein and nucleic acid biosynthesis. Vitamin B<sub>12</sub> is important for hematopoiesis, central nervous system myelination, and mental and psychomotor development.

**Dietary sources** of vitamin B<sub>12</sub> are almost exclusively from animal foods. Organ meats, muscle meats, sea foods (mollusks, oysters, fish), poultry, and egg yolk are rich sources. Fortified ready-to-eat cereals and milk and their products are the important sources of the vitamin for vegetarians. Human milk is an adequate source for breastfeeding infants if the maternal serum B<sub>12</sub> levels are adequate. The vitamin is absorbed from ileum at alkaline pH after binding with intrinsic factor. Enterohepatic circulation, direct absorption, and synthesis by intestinal bacteria are additional mechanisms helping to maintain the vitamin B<sub>12</sub> nutriture.

**Deficiency**

Vitamin B<sub>12</sub> deficiency because of inadequate dietary intake occurs primarily in persons consuming strict vegetarian or vegan diets. Prevalence of vitamin B<sub>12</sub> deficiency is high in predominantly vegetarian or lactovegetarian populations. Breastfeeding infants of B<sub>12</sub>-deficient mothers are also at risk for significant deficiency. Malabsorption of B<sub>12</sub> occurs in celiac disease, ileal resections, Crohn disease, *Helicobacter pylori* infection, and autoimmune atrophic gastritis (pernicious anemia). Use of proton pump inhibitors and/or histamine 2 receptor antagonists may increase the risk of deficiency. Hereditary intrinsic factor deficiency and Imerslund-Gräsbeck disease are inborn errors of metabolism leading to vitamin B<sub>12</sub> malabsorption. Mutations in the hereditary intrinsic factor gene cause hereditary intrinsic factor deficiency, whereas mutations in any of the 2 subunits (cubulin and amnionless) of the intrinsic factor receptor cause Imerslund-Gräsbeck disease.

**Clinical Manifestations**

The hematologic manifestations of vitamin B<sub>12</sub> deficiency are similar to manifestations of folate deficiency and are discussed in Chapter 454.2. Irritability, hypotonia, developmental delay, developmental regression, and involuntary movements are the common neurologic symptoms in infants and children, whereas sensory deficits, paresthesias, and peripheral neuritis are seen in adults. Hyperpigmentation of the knuckles (Fig. 49-6) and palms is another common observation with B<sub>12</sub> deficiency in children. Maternal B<sub>12</sub> deficiency may also be an independent risk factor for fetal neural tube defects.
Bibliography


**Diagnosis**
See Chapter 454.2.

**Treatment**
The hematologic symptoms respond promptly to parenteral administration of 250-1,000 µg vitamin B₁₂. Children with severe deficiency and those with neurologic symptoms need repeated doses; daily or alternate days in first week followed by weekly for the first 1-2 mo, and then monthly thereafter. Children having only hematologic presentation recover fully within 2-3 mo, whereas those with neurologic disease need at least 6 mo of therapy. Children with continuing malabsorptive state, and those having inborn errors of vitamin B₁₂ malabsorption need lifelong treatment. Prolonged daily treatment with high dose (1,000-2,000 µg) oral vitamin B₁₂ preparations has also been found to be equally effective in achieving hematologic and neurologic responses in the elderly, but the data are inadequate in children and young adults.

**Prevention**
The DRIs are 0.4 µg/day at age 0-6 mo, 0.5 µg/day at age 6-12 mo, 0.9 µg/day at age 1-3 yr, 1.2 µg/day at age 4-8 yr, 1.8 µg/day at age 9-13 yr, 2.4 µg/day at age 14-18 yr and in adults, 2.6 µg/day in pregnancy, and 2.8 µg/day in lactation. Pregnant and breastfeeding women should ensure an adequate consumption of animal products to prevent the deficiency in infants. Strict vegetarians, especially vegans, should ensure regular consumption of vitamin B₁₂. Food fortification with the vitamin helps to prevent deficiency in predominantly vegetarian populations.

*Bibliography is available at Expert Consult.*
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Bibliography
Chapter 50  •  Vitamin C (Ascorbic Acid)  329

Chapter 50  
Vitamin C (Ascorbic Acid)  
Dheeraj Shah and H.P.S. Sachdev

Absorption of vitamin C occurs in the upper small intestine by an active process or by simple diffusion when large amounts are ingested. Vitamin C is not stored in the body but is taken up by all tissues; the highest levels are found in the pituitary and adrenal glands. The brain ascorbate content in the fetus and neonate is manyfold higher than the content in the adult brain, a finding probably related to its function in neurotransmitter synthesis.

When a mother’s intake of vitamin C during pregnancy and lactation is adequate, the newborn will have adequate tissue levels of vitamin C related to active placental transfer, subsequently maintained by the vitamin C in breast milk or commercial infant formulas. Breast milk contains sufficient vitamin C to prevent deficiency throughout infancy. Infants consuming pasteurized or boiled animal milk are at significant risk of developing deficiency if the other sources of vitamin C are also lacking in the diet. Neonates whose feeding has been delayed because of clinical condition can also suffer from ascorbic acid deficiency. For patients on total parenteral nutrition, a parenteral dose of 80 mg/day is recommended for full-term infants and a parenteral dose of 25 mg/kg/day is recommended for preterm infants. Children who choose a limited diet or those on fad diets are at risk for vitamin C deficiency.

DEFICIENCY

A deficiency of vitamin C results in the clinical presentation of scurvy, the oldest nutritional deficiency disease to be recognized. Children fed predominantly heat-treated (ultrahigh-temperature or pasteurized) milk or unfortified formulas and not receiving fruits and fruit juices are at significant risk for symptomatic disease. In scurvy, there is defective formation of connective tissues and collagen in skin, cartilage, dentine, bone, and blood vessels, leading to their fragility. In the long bones, osteoid is not deposited by osteoblasts, cortex is thin, and the trabeculae become brittle and fracture easily.

Clinical Features

The early manifestations are irritability, loss of appetite, low-grade fever, musculoskeletal pain, and tenderness in the legs. These signs and symptoms are followed by leg swelling—most marked at the knees and the ankles—and pseudoparalysis. The infant might lie with the hips and knees semiflexed and the feet rotated outward. Subperiosteal hemorrhages in the lower limb bones sometimes acutely increase the swelling and pain, and the condition might mimic acute osteomyelitis or arthritis. A "rosary" at the costochondral junctions and depression of the sternum are other typical features (Fig. 50-1). The angulation of scurbotic beads is usually sharper than the angulation of a rachitic rosary. Gum changes are seen in older children after teeth have erupted and are manifested as bluish purple, spongy swellings of the mucous membrane, especially over the upper incisors (Fig. 50-2). Anemia, a common finding in infants and young children with scurvy, is related to impaired iron absorption and coexistent hematopoietic nutrient deficiencies including iron, vitamin B₁₂, and folate. Hemorrhagic
manifestations of scurvy include petechiae, purpura, and ecchymoses at pressure points; epistaxis; gum bleeding; and the characteristic perifollicular hemorrhages (Fig. 50-3). Other manifestations are poor wound and fracture healing, hyperkeratosis of hair follicles, arthralgia, and muscle weakness.

**Laboratory Findings and Diagnosis**

The diagnosis of vitamin C deficiency is usually based on the characteristic clinical picture, the radiographic appearance of the long bones, and a history of poor vitamin C intake. The typical radiographic changes occur at the distal ends of the long bones and are particularly common at the knees. The shafts of the long bones have a ground-glass appearance because of trabecular atrophy. The cortex is thin and dense, giving the appearance of pencil outlining of the diaphysis and epiphysis. The white line of Fränkel, an irregular but thickened white line at the metaphysis, represents the zone of well-calcified cartilage. The epiphyseal centers of ossification also have a ground-glass appearance and are surrounded by a sclerotic ring (Fig. 50-4). The more specific but late radiologic feature of scurvy is a zone of rarefaction under the white line at the metaphysis. This zone of rarefaction (Trümmerfeld zone), a linear break in the bone that is proximal and parallel to the white line, represents area of debris of broken-down bone trabeculae and connective tissue. A Pelkan spur is a lateral prolongation of the white line and may be present at cortical ends. Epiphyseal separation can occur along the line of destruction, with either linear displacement or compression of the epiphysis against the shaft (Fig. 50-5). Subperiosteal hemorrhages are not visible using plain radiographs during the active phase of scurvy. However, during healing the elevated periosteum becomes calcified and radiopaque (Fig. 50-5), sometimes giving a dumbbell or club shape to the affected bone. MRI can demonstrate acute as well as healing subperiosteal hematomas along with periostitis, metaphyseal changes, and heterogeneous bone marrow signal intensity, even in absence of changes in plain radiographs. Gelatinous transformation of bone marrow, on aspiration, has been reported in children where the procedure was done on suspicion of a malignancy.

Biochemical tests are not very useful in the diagnosis of scurvy, because they do not reflect the tissue status. A plasma ascorbate concentration of <0.2 mg/dL usually is considered deficient. Leukocyte concentration of vitamin C is a better indicator of body stores, but this measurement is technically more difficult to perform. Leukocyte concentrations of ≤10 µg/10⁸ white blood cells are considered deficient and indicate latent scurvy, even in the absence of clinical signs of deficiency. Saturation of the tissues with vitamin C can be estimated from the urinary excretion of the vitamin after a test dose of ascorbic acid. In healthy children, 80% of the test dose appears in the urine within 3-5 hr after parenteral administration. Generalized nonspecific aminoaciduria is common in scurvy, whereas plasma amino acid levels remain normal.

**Differential Diagnosis**

Scurvy is often misdiagnosed as arthritis, osteomyelitis, nonaccidental trauma (child abuse), or acrodynia. The early irritability and bone pain are sometimes attributed to nonspecific pains or other nutritional deficiencies. Copper deficiency results in a radiographic picture very
similar to that of scurvy. Henoch-Schönlein purpura, thrombocytopenic purpura, or leukemia is sometimes suspected in children presenting with hemorrhagic manifestations.

**Treatment**
Vitamin C supplements of 100-200 mg/day orally or parenterally ensure rapid and complete cure. The clinical improvement is seen within a week in most cases, but the treatment should be continued for up to 3 mo for complete recovery.

**Prevention**
Breastfeeding protects against vitamin C deficiency throughout infancy. In children consuming milk formula, fortification with vitamin C must be ensured. Children consuming heat-treated milk should consume adequate vitamin C–rich foods in infancy. Dietary or medicinal supplements are required in severely malnourished children, and chronic debilitating conditions such as malignancies and neurologic disorders.

**TOXICITY**
Daily intake of <2 g of vitamin C is generally without adverse effects in adults. Larger doses can cause gastrointestinal problems, such as abdominal pain and osmotic diarrhea. Megadoses of vitamin C should be avoided in patients with a history of urolithiasis or conditions related to excessive iron accumulation such as thalassemia and hemochromatosis. There is a paucity of data regarding vitamin C toxicity in children. The following values for tolerable upper intake levels are extrapolated from data for adults based on body weight differences: age 1-3 yr, 400 mg; age 4-8 yr, 650 mg; age 9-13 yr, 1,200 mg; and age 14-18 yr, 1,800 mg.

*Bibliography is available at Expert Consult.*
Bibliography


RICKETS

Bone consists of a protein matrix called osteoid and a mineral phase, principally composed of calcium and phosphate, mostly in the form of hydroxyapatite. Osteomalacia is present when there is inadequate mineralization of bone osteoid and occurs in children and adults. Rickets is a disease of growing bone that is caused by unmineralized matrix at the growth plates and occurs in children only before fusion of the epiphyses. Because growth plate cartilage and osteoid continue to expand but mineralization is inadequate, the growth plate thickens. There is also an increase in the circumference of the growth plate and the metaphysis, increasing bone width at the location of the growth plates and causing some of the classic clinical manifestations, such as widening of the wrists and ankles. There is a general softening of the bones that causes them to bend easily when subject to forces such as weight bearing or muscle pull. This softening leads to a variety of bone deformities.

Rickets is principally caused by vitamin D deficiency (Table 51-1) and was rampant in northern Europe and the United States during the early years of the 20th century. Although this problem was largely corrected through public health measures that provided children with adequate vitamin D, rickets remains a persistent problem in developed countries, with many cases still secondary to preventable nutritional vitamin D deficiency. It remains a significant problem in developing countries, and may be secondary to nutritional vitamin D deficiency and inadequate intake of calcium.

Etiology

There are many causes of rickets (Table 51-2), including vitamin D disorders, calcium deficiency, phosphorous deficiency, and distal renal tubular acidosis.

Clinical Manifestations

Most manifestations of rickets are a result of skeletal changes (Table 51-3). Craniotabes is a softening of the cranial bones and can be detected by applying pressure at the occiput or over the parietal bones. The sensation is similar to the feel of pressing into a ping-pong ball and then releasing. Craniotabes may also be secondary to osteogenesis imperfecta, hydrocephalus, and syphilis. It is a normal finding in many newborns, especially near the suture lines, but it typically disappears within a few months of birth. Widening of the costochondral junctions results in a rachitic rosary, which feels like the beads of a rosary as the examiner’s fingers move along the costochondral junctions from rib to rib (Fig. 51-1). Growth plate widening is also responsible for the enlargement at the wrists and ankles. The horizontal depression along the lower anterior chest known as Harrison groove occurs from pulling of the softened ribs by the diaphragm during inspiration (Fig. 51-2). Softening of the ribs also impairs air movement and predisposes patients to atelectasis and pneumonia.

There is some variation in the clinical presentation of rickets based on the etiology. Changes in the lower extremities tend to be the dominant feature in X-linked hypophosphatemic rickets. Symptoms secondary to hypocalcemia occur only in those forms of rickets associated with decreased serum calcium (Table 51-4).

The chief complaint in a child with rickets is quite variable. Many children present because of skeletal deformities, whereas others have difficulty walking owing to a combination of deformity and weakness. Other common presenting complaints include failure to thrive and symptomatic hypocalcemia (see Chapter 572).
Part VI
Nutrition

Table 51-1 Physical and Metabolic Properties and Food Sources of the Vitamins (D, E, and K)

<table>
<thead>
<tr>
<th>NAMES AND SYNONYMS</th>
<th>CHARACTERISTICS</th>
<th>BIOCHEMICAL ACTION</th>
<th>EFFECTS OF DEFICIENCY</th>
<th>EFFECTS OF EXCESS</th>
<th>SOURCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>VITAMIN D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D&lt;sub&gt;1&lt;/sub&gt; (3-cholecalciferol), which is synthesized in the skin, and vitamin D&lt;sub&gt;2&lt;/sub&gt; (from plants or yeast) are biologically equivalent; 1 µg = 40 IU vitamin D</td>
<td>Fat-soluble, stable to heat, acid alkali, and oxidation; bile necessary for absorption; hydroxylation in the liver and kidney necessary for biologic activity</td>
<td>Necessary for GI absorption of calcium; also increases absorption of phosphate; direct actions on bone, including mediating resorption</td>
<td>Rickets in growing children; osteomalacia; hypocalcemia can cause tetany and seizures</td>
<td>Hypercalcemia, which can cause emesis, anorexia, pancreatitis, hypertension, arrhythmias, CNS effects, polyuria, nephrolithiasis, renal failure</td>
<td>Exposure to sunlight (UV light); fish oils, fatty fish, egg yolks, and vitamin D–fortified formula, milk, cereals, bread</td>
</tr>
<tr>
<td>VITAMIN E</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Group of related compounds with similar biologic activities; α-tocopherol is the most potent and the most common form</td>
<td>Fat-soluble; readily oxidized by oxygen, iron, rancid fats; bile acids necessary for absorption</td>
<td>Antioxidant; protection of cell membranes from lipid peroxidation and formation of free radicals</td>
<td>Red cell hemolysis in premature infants; posterior column and cerebellar dysfunction; pigmentary retinopathy</td>
<td>Unknown</td>
<td>Vegetable oils, seeds, nuts, green leafy vegetables, margarine</td>
</tr>
<tr>
<td>VITAMIN K</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group of naphthoquinones with similar biologic activities; K&lt;sub&gt;1&lt;/sub&gt; (phyloquinone) from diet; K&lt;sub&gt;2&lt;/sub&gt; (menaquinones) from intestinal bacteria</td>
<td>Natural compounds are fat-soluble; stable to heat and reducing agents; labile to oxidizing agent, strong acids, alkali, light; bile salts necessary for intestinal absorption</td>
<td>Vitamin K–dependent proteins include coagulation factors II, VII, IX, and X; proteins C, S, Z; matrix Gla protein, osteocalcin</td>
<td>Hemorrhagic manifestations; long-term bone and vascular health</td>
<td>Not established; analogs (no longer used) caused hemolytic anemia, jaundice, kernicterus, death</td>
<td>Green leafy vegetables, liver, certain legumes and plant oils; widely distributed</td>
</tr>
</tbody>
</table>

Table 51-2 Causes of Rickets

<table>
<thead>
<tr>
<th>VITAMIN D DISORDERS</th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutritional vitamin D deficiency</td>
<td>Congenital vitamin D deficiency</td>
<td>Secondary vitamin D deficiency</td>
<td>Malabsorption</td>
<td>Increased degradation</td>
<td>Decreased liver 25-hydroxylase</td>
</tr>
<tr>
<td>Vitamin D–dependent rickets type 1 A and B</td>
<td>Vitamin D–dependent rickets type 2 A and B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CALCIUM DEFICIENCY</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Low intake</td>
<td>Diet</td>
<td>Premature infants (rickets of prematurity)</td>
<td>Malabsorption</td>
<td>Primary disease</td>
<td>Dietary inhibitors of calcium absorption</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PHOSPHORUS DEFICIENCY</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate intake</td>
<td>Premature infants (rickets of prematurity)</td>
<td>Aluminum-containing antacids</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RENAL LOSSES</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>X-linked hypophosphatemic rickets*</td>
<td>Autosomal dominant hypophosphatemic rickets*</td>
<td>Autosomal recessive hypophosphatemic rickets (1 and 2)*</td>
<td>Hereditary hypophosphatemic rickets with hypercalcemia</td>
<td>Overproduction of fibroblast growth factor-23</td>
<td>Tumor-induced rickets*</td>
</tr>
<tr>
<td>McCune-Albright syndrome*</td>
<td>Epidermal nevus syndrome*</td>
<td>Neurofibromatosis*</td>
<td>Fanconi syndrome</td>
<td>Dent disease</td>
<td>Distal renal tubular acidosis</td>
</tr>
</tbody>
</table>

Table 51-3 Clinical Features of Rickets

<table>
<thead>
<tr>
<th>GENERAL</th>
<th>Failure to thrive</th>
<th>Listlessness</th>
<th>Protruding abdomen</th>
<th>Muscle weakness (especially proximal)</th>
<th>Fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEAD</td>
<td>Craniotabes</td>
<td>Frontal bossing</td>
<td>Delayed fontanel closure</td>
<td>Delayed dentition; caries</td>
<td>Craniosynostosis</td>
</tr>
<tr>
<td>CHEST</td>
<td>Rachitic rosary</td>
<td>Harrison groove</td>
<td>Respiratory infections and atelectasis†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BACK</td>
<td>Scoliosis</td>
<td>Kyphosis</td>
<td>Lordosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXTREMITIES</td>
<td>Enlargement of wrists and ankles</td>
<td>Valgus or varus deformities</td>
<td>Windsbet deformity (combination of valgus deformity of 1 leg with varus deformity of the other leg)</td>
<td>Anterior bowing of the tibia and femur</td>
<td>Coxa vara</td>
</tr>
</tbody>
</table>

| HYPOCALCEMIC SYMPTOMS† | Tetany | Seizures | Stridor due to laryngeal spasm |

*Disorders secondary to excess fibroblast growth factor-23.
†These features are most commonly associated with the vitamin D–deficiency disorders.
‡These symptoms develop only in children with disorders that produce hypocalcemia (see Table 51-4).
Radiology
Rachitic changes are most easily visualized on posteroanterior radiographs of the wrist, although characteristic rachitic changes can be seen at other growth plates (Figs. 51-3 and 51-4). Decreased calcification leads to thickening of the growth plate. The edge of the metaphysis loses its sharp border, which is described as fraying. The edge of the metaphysis changes from a convex or flat surface to a more concave surface. This change to a concave surface is termed cupping and is most easily seen at the distal ends of the radius, ulna, and fibula. There is widening of the distal end of the metaphysis, corresponding to the clinical observation of thickened wrists and ankles, as well as the rachitic rosary. Other radiologic features include coarse trabeculation of the diaphysis and generalized rarefaction.

Diagnosis
Most cases of rickets are diagnosed based on the presence of classic radiographic abnormalities. The diagnosis is supported by physical examination findings (see Table 51-3) and a history and laboratory test results that are consistent with a specific etiology.

Clinical Evaluation
Because the majority of children with rickets have a nutritional deficiency, the initial evaluation should focus on a dietary history, emphasizing intake of vitamin D and calcium. Most children in industrialized nations receive vitamin D from formula, fortified milk, or vitamin supplements. Along with the amount, the exact composition of the formula or milk is pertinent, because rickets has occurred in children given products that are called milk (e.g., soy milk) but are deficient in vitamin D and/or minerals.

Cutaneous synthesis mediated by sunlight exposure is an important source of vitamin D. It is important to ask about time spent outside, sunscreen use, and clothing, especially if there may be a cultural reason for increased covering of the skin. Because winter sunlight is ineffective at stimulating cutaneous synthesis of vitamin D, the season is an additional consideration. Children with increased skin pigmentation are at increased risk for vitamin D deficiency because of decreased cutaneous synthesis.

The presence of maternal risk factors for nutritional vitamin D deficiency, including diet and sun exposure, is an important consideration when a neonate or young infant has rachitic findings, especially if the infant is breastfed. Determining a child's intake of dairy products, the main dietary source of calcium, provides a general sense of calcium intake. High dietary fiber can interfere with calcium absorption.

The child's medication use is relevant, because certain medications, such as the anticonvulsants phenobarbital and phenytoin, increase degradation of vitamin D, and aluminum-containing antacids interfere with the absorption of phosphate.

Malabsorption of vitamin D is suggested by a history of liver or intestinal disease. Undiagnosed liver or intestinal disease should be suspected if the child has gastrointestinal (GI) symptoms, although occasionally rickets is the presenting complaint. Fat malabsorption is
often associated with diarrhea or oily stools, and there may be signs or symptoms suggesting deficiencies of other fat-soluble vitamins (A, E, and K; see Chapters 48, 52, and 53).

A history of renal disease (proteinuria, hematuria, urinary tract infections) is an additional significant consideration, given the importance of chronic kidney disease as a cause of rickets. Polyuria can occur in children with chronic kidney disease or Fanconi syndrome.

Children with rickets might have a history of dental caries, poor growth, delayed walking, waddling gait, pneumonia, and hypocalcemic symptoms.

The family history is critical, given the large number of genetic causes of rickets, although most of these causes are rare. Along with bone disease, it is important to inquire about leg deformities, difficulties with walking, or unexplained short stature, because some parents may be unaware of their diagnosis. Undiagnosed disease in the mother is not unusual in X-linked hypophosphatemia. A history of a unexplained sibling death during infancy may be present in the child with cystinosis, the most common cause of Fanconi syndrome in children.

The physical examination focuses on detecting manifestations of rickets (see Table 51-3). It is important to observe the child’s gait, auscultate the lungs to detect atelectasis or pneumonia, and plot the patient’s growth. Alopecia suggests vitamin D–dependent rickets type 2.

The initial laboratory tests in a child with rickets should include serum calcium, phosphorus, alkaline phosphatase, parathyroid hormone (PTH), 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, creatinine, and electrolytes (see Tables 51-4 and 51-5 for interpretation). Urinalysis is useful for detecting the glycosuria and aminoaciduria (positive dipstick for protein) seen with Fanconi syndrome. Evaluation of urinary excretion of calcium (24 hr collection for calcium or calcium: creatinine ratio) is helpful if hereditary hypophosphatemic rickets with hypercalciuria or Fanconi syndrome is suspected. Direct measurement of other fat-soluble vitamins (A, E, and

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Figure 51-3 Wrist x-rays in a normal child (A) and in a child with rickets (B). The child with rickets has metaphyseal fraying and cupping of the distal radius and ulna.

Figure 51-4 X-rays of the knees in a 7 yr old girl with distal renal tubular acidosis and rickets. A, At initial presentation, there is widening of the growth plate and metaphysical fraying. B, Dramatic improvement after 4 mo of therapy with alkali.
### Table 51-5 | Biochemical Changes in Genetic Causes of Rickets

<table>
<thead>
<tr>
<th>SERUM BIOCHEMISTRY</th>
<th>URINE BIOCHEMISTRY</th>
<th>OTHER FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate</td>
<td>Calcium</td>
<td>PTH</td>
</tr>
<tr>
<td><strong>HYPOCALCEMIC VITAMIN D PATHWAY DEFECTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
<td>Low</td>
<td>Variable</td>
</tr>
<tr>
<td>VDDR1B</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>VDDR1A</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>VDDR2A</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>VDDR2B</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td><strong>HYPOPHOSPHATEMIC RICKETS WITH RAISED FGF23</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XLH</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td>ADHR</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td>ARHR1</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td>ARHR2</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>HYPOPHOSPHATEMIC RICKETS WITHOUT RAISED FGF23</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dent's disease*</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td>HHRH</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td>αKlotho mutation</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>OTHER INHERITED RACHITIC DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPP (severe)</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>HPP (mild)</td>
<td>Normal or high</td>
<td>Normal or high</td>
</tr>
</tbody>
</table>


PTH, parathyroid hormone; 250HD, calcidiol; 1,250H₂D, calcitriol; FGF23, fibroblast growth factor 23; Alk phos, alkaline phosphatase; NA, data not available; VDDR1B, vitamin D–dependent rickets due to defects in CYP2R1 encoding vitamin D 25-hydroxylase; VDDR1A, vitamin D–dependent rickets due to defects in CYP27B1 encoding 25-hydroxyvitamin D-1alpha hydroxylase; ND, not detected; VDDR2A, vitamin D–dependent rickets due to defects in VDR encoding the vitamin D receptor; VDDR2B, vitamin D–dependent rickets due to defects in HNRNPC encoding hnRNPC1 and hnRNPC2; XLH, X-linked hypophosphatemic rickets due to mutations in PHEX; ADHR, autosomal dominant hypophosphatemic rickets due to mutations in FGF23; ARHR1, autosomal recessive hypophosphatemic rickets due to mutations in DMP1; ARHR2, autosomal recessive hypophosphatemic rickets due to mutations in ENPP1; HHRH, hereditary hypophosphatemic rickets with hypercalciumia due to mutations in SLC34A3; HPP, hypophosphatasia.

*Denis disease is due to mutations in CLCN7.
K) or indirect assessment of deficiency (prothrombin time for vitamin D deficiency) is appropriate if malabsorption is a consideration.

**VITAMIN D DISORDERS**

**Vitamin D Physiology**

Vitamin D can be synthesized in skin epithelial cells and therefore technically is not a vitamin. Cutaneous synthesis is normally the most important source of vitamin D and depends on the conversion of 7-dehydrocholesterol to vitamin D₃ (3-cholecalciferol) by ultraviolet B radiation from the sun. The efficiency of this process is decreased by melanin; hence, more sun exposure is necessary for vitamin D synthesis in people with increased skin pigmentation. Measures to decrease sun exposure, such as covering the skin with clothing or applying sunscreen, also decrease vitamin D synthesis. Children who spend less time outside have reduced vitamin D synthesis. The winter sun away from the equator is ineffective at mediating vitamin D synthesis.

There are few natural dietary sources of vitamin D. Fish liver oils have a high vitamin D content. Other good dietary sources include fatty fish and egg yolks. Most children in industrialized countries receive vitamin D via fortified foods, especially formula and milk (both of which contain 400 IU/L) and some breakfast cereals and breads. Supplemental vitamin D may be vitamin D₃ (which comes from plants or yeast) or vitamin D₂. Breast milk has a low vitamin D content, approximately 12-60 IU/L.

Vitamin D is transported bound to vitamin D-binding protein to the liver, where 25-hydroxylase converts vitamin D into 25-hydroxyvitamin D (25-(D)), the most abundant circulating form of vitamin D. Because there is little regulation of this liver hydroxylase step, measurement of 25-D is the standard method for determining a patient’s vitamin D status. The final step in activation occurs in the kidney, where 1α-hydroxylase adds a second hydroxyl group, resulting in 1,25-D. The 1α-hydroxylase is upregulated by PTH and hypophosphatemia; hyperphosphatemia and 1,25-D inhibit this enzyme. Most 1,25-D circulates bound to vitamin D-binding protein.

1,25-D acts by binding to an intracellular receptor, and the complex affects gene expression by interacting with vitamin D-responsive elements. In the intestine, this binding results in a marked increase in calcium absorption, which is highly dependent on 1,25-D. There is also an increase in phosphorus absorption, but this effect is less significant because most dietary phosphorus absorption is vitamin D independent. 1,25-D also has direct effects on bone, including mediating resorption. 1,25-D directly suppresses PTH secretion by the parathyroid gland, thus completing a negative feedback loop. PTH secretion is also suppressed by the increase in serum calcium mediated by 1,25-D. 1,25-D inhibits its own synthesis in the kidney and increases the synthesis of inactive metabolites.

**Nutritional Vitamin D Deficiency**

Vitamin D deficiency remains the most common cause of rickets globally and is prevalent, even in industrialized countries. Because vitamin D can be obtained from dietary sources or from cutaneous synthesis, most patients in industrialized countries have a combination of risk factors that lead to vitamin D deficiency.

**Etiology**

Vitamin D deficiency most commonly occurs in infancy because of a combination of poor intake and inadequate cutaneous synthesis. Transplacental transport of vitamin D, mostly 25-D, typically provides enough vitamin D for the 1st 2 mo of life unless there is severe maternal vitamin D deficiency. Infants who receive formula receive adequate vitamin D, even without cutaneous synthesis. Because of the low vitamin D content of breast milk, breastfed infants rely on cutaneous synthesis or vitamin supplements. Cutaneous synthesis can be limited because of the ineffectiveness of the winter sun in stimulating vitamin D synthesis; avoidance of sunlight because of concerns about cancer, neighborhood safety, or cultural practices; and decreased cutaneous synthesis because of increased skin pigmentation.

The effect of skin pigmentation explains why most cases of nutritional rickets in the United States and northern Europe occur in breastfed children of African descent or other dark-pigmented populations. The additional impact of the winter sun is supported by the fact that such infants more commonly present in the late winter or spring. In some groups, complete covering of infants or the practice of not taking infants outside has a significant role, explaining the occurrence of rickets in infants living in areas of abundant sunshine, such as the Middle East. Because the mothers of some infants can have the same risk factors, decreased maternal vitamin D can also contribute, both by leading to reduced vitamin D content in breast milk and by lessening transplacental delivery of vitamin D. Rickets caused by vitamin D deficiency can also be secondary to unconventional dietary practices, such as vegan diets that use unfortified soy milk or rice milk.

**Clinical Manifestations**

The clinical features are typical of rickets (see Table 51-3), with a significant minority presenting with symptoms of hypocalcemia; prolonged laryngospasm is occasionally fatal. These children have an increased risk of pneumonia and muscle weakness leading to a delay in motor development.

**Laboratory Findings**

Tables 51-4 and 51-5 summarize the principal laboratory findings. Hypocalcemia is a variable finding as a result of the actions of the elevated PTH to increase the serum calcium concentration. The hypophosphatemia is caused by PTH-induced renal losses of phosphate, combined with a decrease in intestinal absorption.

The wide variation in 1,25-D levels (low, normal, or high) is secondary to the upregulation of renal 1α-hydroxylase caused by concurrent hypophosphatemia and hyperparathyroidism. Because serum levels of 1,25-D are much lower than the levels of 25-D, even with low levels of 25-D there is still often enough 25-D present to act as a precursor for 1,25-D synthesis in the presence of an upregulated 1α-hydroxylase. The level of 1,25-D is only low when there is severe vitamin D deficiency.

Some patients have a metabolic acidosis secondary to PTH-induced renal bicarbonate wasting. There may also be generalized aminoaciduria.

**Diagnosis and Differential Diagnosis**

The diagnosis of nutritional vitamin D deficiency is based on the combination of a history of poor vitamin D intake and risk factors for decreased cutaneous synthesis, radiographic changes consistent with rickets, and typical laboratory findings (see Tables 51-4 and 51-5). A normal PTH level almost never occurs with vitamin D deficiency and suggests a primary phosphate disorder.

**Treatment**

Children with nutritional vitamin D deficiency should receive vitamin D and adequate nutritional intake of calcium and phosphorus. There are 2 strategies for administration of vitamin D. With stoss therapy, 300,000-600,000 IU of vitamin D are administered orally or intramuscularly as 2-4 doses over 1 day. Because the doses are observed, stoss therapy is ideal in situations where adherence to therapy is question-able. The alternative is daily, high-dose vitamin D, with doses ranging from 2,000-5,000 IU/day over 4-6 wk. Either strategy should be followed by daily vitamin D intake of 400 IU/day if <1 yr old or 600 IU/day if >1 yr old. It is important to ensure that children receive adequate dietary calcium and phosphorus; this dietary intake is usually provided by milk, formula, and other dairy products.

Children who have symptomatic hypocalcemia might need intravenous calcium acutely, followed by oral calcium supplements, which typically can be tapered over 2-6 wk in children who receive adequate dietary calcium. Transient use of intravenous or oral 1,25-D (calcitriol) is often helpful in reversing hypocalcemia in the acute phase by providing active vitamin D during the delay as supplemental vitamin D is converted to active vitamin D. Calcitriol doses are typically 0.05 µg/kg/day. Intravenous calcium is initially given as an acute bolus for symptomatic hypocalcemia (20 mg/kg of calcium.
chloride or 100 mg/kg of calcium gluconate). Some patients require a continuous intravenous calcium drip, titrated to maintain the desired serum calcium level. These patients should transition to enteral calcium, and most infants require approximately 1,000 mg of elemental calcium.

**Prognosis**

Most children have an excellent response to treatment, with radiologic healing occurring within a few months. Laboratory test results should also normalize rapidly. Many of the bone malformations improve dramatically, but children with severe disease can have permanent deformities and short stature. Rarely, patients benefit from orthopedic intervention for leg deformities, although this is generally not done until the metabolic bone disease has healed, there is clear evidence that the deformity will not self-resolve, and the deformity is causing functional problems.

**Prevention**

Most cases of nutritional rickets can be prevented by universal administration of 400 IU of vitamin D to infants who are breastfed. Older children should receive 600 IU/day. Vitamin D may be administered as a component of a multivitamin or as a vitamin D supplement.

**Congenital Vitamin D Deficiency**

Congenital rickets is quite rare in industrialized countries and occurs when there is severe maternal vitamin D deficiency during pregnancy. Maternal risk factors include poor dietary intake of vitamin D, lack of adequate sun exposure, and closely spaced pregnancies. These newborns can have symptomatic hypocalcemia, intrauterine growth retardation, and decreased bone ossification, along with classic rachitic changes. More subtle maternal vitamin D deficiency can have an adverse effect on neonatal bone density and birthweight, cause a defect in dental enamel, and predispose infants to neonatal hypocalcemic tetany. Treatment of congenital rickets includes vitamin D supplementation and adequate intake of calcium and phosphorus. Use of prenatal vitamins containing vitamin D prevents this entity.

**Secondary Vitamin D Deficiency**

Etiology

Along with inadequate intake, vitamin D deficiency can develop due to inadequate absorption, decreased hydroxylation in the liver, and increased degradation. Because vitamin D is fat-soluble, its absorption may be decreased in patients with a variety of liver and GI diseases, including cholestatic liver disease, defects in bile acid metabolism, cystic fibrosis and other causes of pancreatic dysfunction, celiac disease, and Crohn disease. Malabsorption of vitamin D can also occur with intestinal lymphangiectasia and after intestinal resection.

Severe liver disease, which is usually also associated with malabsorption, can cause a decrease in 25-D formation as a consequence of insufficient enzyme activity. Because of the large reserve of 25-hydroxylase activity in the liver, vitamin D deficiency as a result of liver disease usually requires a loss of >90% of liver function. A variety of medications increase the degradation of vitamin D by inducing the cytochrome P450 system. Rickets as a consequence of vitamin D deficiency can develop in children receiving anticonvulsants, such as phenobarbital or phenytoin, or antituberculosis medications, such as isoniazid or rifampin.

**Treatment**

Treatment of vitamin D deficiency attributable to malabsorption requires high doses of vitamin D. Because of its better absorption, 25-D (25-50 µg/day or 5-7 µg/kg/day) is superior to vitamin D₃. The dose is adjusted based on monitoring of serum levels of 25-D. Alternatively, patients may be treated with 1,25-D, which also is better absorbed in the presence of fat malabsorption, or with parenteral vitamin D. Children with rickets as a result of increased degradation of vitamin D by the cytochrome P450 system require the same acute therapy as indicated for nutritional deficiency (discussed earlier), followed by long-term administration of high doses of vitamin D (e.g., 1,000 IU/day), with dosing titrated based on serum levels of 25-D. Some patients require as much as 4,000 IU/day.

**Vitamin D–Dependent Rickets, Type 1**

Children with vitamin D–dependent rickets type 1, an autosomal recessive disorder, have mutations in the gene encoding renal 1α-hydroxylase, preventing conversion of 25-D into 1,25-D. These patients normally present during the 1st-2yr of life and can have any of the classic features of rickets (see Table 51-3), including asymptomatic hypocalcemia. They have normal levels of 25-D, but low levels of 1,25-D (see Table 51-5). Occasionally, 1,25-D levels are at the lower limit of normal, inappropriately low given the high PTH and low serum phosphorus levels, both of which should increase the activity of renal 1α-hydroxylase and cause elevated levels of 1,25-D. As in nutritional vitamin D deficiency, renal tubular dysfunction can cause a metabolic acidosis and generalized aminoaciduria.

**Treatment**

These patients respond to long-term treatment with 1,25-D (calcitriol). Initial doses are 0.25-2 µg/day, and lower doses are used once the rickets has healed. Especially during initial therapy, it is important to ensure adequate intake of calcium. The dose of calcitriol is adjusted to maintain a low-normal serum calcium level, a normal serum phosphorus level, and a high-normal serum PTH level. Targeting a low-normal calcium concentration and a high-normal PTH level avoids excessive dosing of calcitriol, which can cause hypercalcemia and nephrocalcinosis. Hence, patient monitoring includes periodic assessment of urinary calcium excretion, with a target of <4 mg/kg/day.

**Vitamin D–Dependent Rickets, Type 2**

Patients with vitamin D–dependent rickets type 2 have mutations in the gene encoding the vitamin D receptor, preventing a normal physiologic response to 1,25-D. Levels of 1,25-D are extremely elevated in this autosomal recessive disorder (see Table 51-4). Most patients present during infancy, although rickets in less severely affected patients might not be diagnosed until adulthood. Less-severe disease is associated with a partially functional vitamin D receptor. Approximately 50-70% of children have alopecia, which tends to be associated with a more severe form of the disease and can range from alopecia areata to alopecia totalis. Epidermal cysts are a less common manifestation.

**Treatment**

Some patients respond to extremely high doses of vitamin D₂, 25-D or 1,25-D, especially patients without alopecia. This response is due to a partially functional vitamin D receptor. All patients with this disorder should be given a 3-6 mo trial of high-dose vitamin D and oral calcium. The initial dose of 1,25-D should be 2 µg/day, but some patients require doses as high as 50-60 µg/day. Calcium doses are 1,000-3,000 mg/day. Patients who do not respond to high-dose vitamin D may be treated with long-term intravenous calcium, with possible transition to very high dose oral calcium supplements. Treatment of patients who do not respond to vitamin D is difficult.

**Chronic Kidney Disease (See Chapter 535.2)**

With chronic kidney disease, there is decreased activity of 1α-hydroxylase in the kidney, leading to diminished production of 1,25-D. In chronic kidney disease, unlike the other causes of vitamin D deficiency, patients have hyperphosphatemia as a result of decreased renal excretion (see Table 51-4).

**Treatment**

Therapy requires the use of a form of vitamin D that can act without 1-hydroxylation by the kidney (calcitriol), which both permits adequate absorption of calcium and directly suppresses the parathyroid gland. Because hyperphosphatemia is a stimulus for PTH secretion, normalization of the serum phosphorus level via a combination of dietary phosphorus restriction and the use of oral phosphate binders is as important as the use of activated vitamin D.
**CALCIUM DEFICIENCY**

**Pathophysiology**
Rickets secondary to inadequate dietary calcium is a significant problem in some countries in Africa, although there are cases in other regions of the world, including industrialized countries. Because breast milk and formula are excellent sources of calcium, this form of rickets develops after children have been weaned from breast milk or formula and is more likely to occur in children who are weaned early. Rickets develops because the diet has low calcium content, typically <200 mg/day. There is little intake of dairy products or other sources of calcium. In addition, because of reliance on grains and green leafy vegetables, the diet may be high in phytate, oxalate, and phosphate, which decrease absorption of dietary calcium. In industrialized countries, rickets caused by calcium deficiency can occur in children who consume an unconventional diet. Examples include children with milk allergy who have low dietary calcium and children who transition from formula or breast milk to juice, soda, or a calcium-poor soy drink, without an alternative source of dietary calcium.

This type of rickets can develop in children who receive intravenous nutrition without adequate calcium. Malabsorption of calcium can occur in celiac disease, intestinal abetalipoproteinemia, and after small bowel resection. There may be concurrent malabsorption of vitamin D.

**Clinical Manifestations**
Children have the classic signs and symptoms of rickets (see Table 51-3). Presentation can occur during infancy or early childhood, although some cases are diagnosed in teenagers. Because calcium deficiency occurs after the cessation of breastfeeding, it tends to occur later than the nutritional vitamin D deficiency that is associated with breastfeeding. In Nigeria, nutritional vitamin D deficiency is most common at 4-15 mo of age, whereas calcium-deficiency rickets typically occurs at 15-25 mo of age.

**Diagnosis**
Laboratory findings include increased levels of alkaline phosphatase, PTH, and 1,25-D (see Table 51-4). Calcium levels may be normal or low, although symptomatic hypocalcemia is uncommon. There is decreased urinary excretion of calcium, and serum phosphorus levels may be low as a result of renal wasting of phosphate from secondary hyperparathyroidism. In some children, there is coexisting nutritional vitamin D deficiency, with low 25-D levels.

**Treatment**
Treatment focuses on providing adequate calcium, typically as a dietary supplement (doses of 700 [1-3 yr age], 1,000 [4-8 yr age], 1,300 [9-18 yr age] mg/day of elemental calcium are effective). Vitamin D supplementation is necessary if there is concurrent vitamin D deficiency (discussed earlier). Prevention strategies include discouraging early cessation of breastfeeding and increasing dietary sources of calcium. In countries such as Kenya, where many children have diets high in cereal with negligible intake of cow's milk, school-based milk programs have been effective in reducing the prevalence of rickets.

**PHOSPHOROUS DEFICIENCY**

**Inadequate Intake**
With the exception of starvation or severe anorexia, it is almost impossible to have a diet that is deficient in phosphorus, because phosphorus is present in most foods. Decreased phosphorus absorption can occur in diseases associated with malabsorption (celiac disease, cystic fibrosis, cholestatic liver disease), but if rickets develops, the primary problem is usually malabsorption of vitamin D and/or calcium.

Isolated malabsorption of phosphorus occurs in patients with long-term use of aluminum-containing antacids. These compounds are very effective at chelating phosphate in the GI tract, leading to decreased absorption. This decreased absorption results in hypophosphatemia with secondary osteomalacia in adults and rickets in children. This entity responds to discontinuation of the antacid and short-term phosphorus supplementation.

**Fibroblast Growth Factor-23**
Fibroblast growth factor-23 (FGF-23) is a humoral mediator that decreases renal tubular reabsorption of phosphate and therefore decreases serum phosphorus. FGF-23, synthesized by osteocytes, also decreases the activity of renal 1α-hydroxylase, resulting in a decrease in the production of 1,25-D. Increased levels of FGF-23 cause many of the renal phosphate-wasting diseases (see Table 51-2).

**X-Linked Hypophosphatemic Rickets**
Among the genetic disorders causing rickets because of hypophosphatemia, X-linked hypophosphatemic rickets (XLH) is the most common, with a prevalence of 1/20,000. The defective gene is on the X chromosome, but female carriers are affected, so it is an X-linked dominant disorder.

**Pathophysiology**
The defective gene is called PHEX because it is a Phosphate-regulating gene with homology to Endopeptidases on the X chromosome. The product of this gene appears to have an indirect role in inactivating FGF-23. Mutations in the PHEX gene lead to increased levels of FGF-23. Because the actions of FGF-23 include inhibition of phosphate reabsorption in the proximal tubule, phosphate excretion is increased. FGF-23 also inhibits renal 1α-hydroxylase, leading to decreased production of 1,25-D.

**Clinical Manifestations**
These patients have rickets, but abnormalities of the lower extremities and poor growth are the dominant features. Delayed dentition and tooth abscesses are also common. Some patients have hypophosphatemia and short stature without clinically evident bone disease.

**Laboratory Findings**
Patients have high renal excretion of phosphate, hypophosphatemia, and increased alkaline phosphatase; PTH and serum calcium levels are normal (see Table 51-4). Hypophosphatemia normally upregulates renal 1α-hydroxylase and should lead to an increase in 1,25-D, but these patients have low or inappropriately normal levels of 1,25-D.

**Treatment**
Patients respond well to a combination of oral phosphorus and 1,25-D (calcitriol). The daily need for phosphorus supplementation is 1-3 g of elemental phosphorus divided into 4-5 doses. Frequent dosing helps to prevent prolonged decrements in serum phosphorus because there is a rapid decline after each dose. In addition, frequent dosing decreases diarrhea, a complication of high-dose oral phosphorus. Calcitriol is administered 30-70 ng/kg/day divided into 2 doses.

Complications of treatment occur when there is not an adequate balance between phosphorus supplementation and calcitriol. Excess phosphorus, by decreasing enteral calcium absorption, leads to secondary hyperparathyroidism, with worsening of the bone lesions. In contrast, excess calcitriol causes hypercalcemia and nephrocalcinosis and can even cause hypercalcinemia. Hence, laboratory monitoring of treatment includes serum calcium, phosphorus, alkaline phosphatase, PTH, and urinary calcium, as well as periodic renal ultrasounds to evaluate patients for nephrocalcinosis. Because of variation in the serum phosphorus level and the importance of avoiding excessive phosphorus dosing, normalization of alkaline phosphatase levels is a more useful method of assessing the therapeutic response than measuring serum phosphorus. For children with significant short stature, growth hormone is an effective option. Children with severe deformities might need osteotomies, but these procedures should be done only when treatment has led to resolution of the bone disease.

**Prognosis**
The response to therapy is usually good, although frequent dosing can lead to problems with compliance. Girls generally have less-severe disease than boys, probably because of the X-linked inheritance. Short stature can persist despite healing of the rickets. Adults generally do well with less-aggressive treatment, and some receive calcitriol alone.
Adults with bone pain or other symptoms improve with oral phosphorus supplementation and calcitriol.

**Autosomal Dominant Hypophosphatemic Rickets**

Autosomal dominant hypophosphatemic rickets (ADHR) is much less common than XLH. There is incomplete penetrance and variable age of onset. Patients with ADHR have a mutation in the gene encoding FGF-23 (FGF23). The mutation prevents degradation of FGF-23 by proteases, leading its level to increase. The actions of FGF-23 include decreased reabsorption of phosphate in the renal proximal tubule, which results in hypophosphatemia, and inhibition of the 1α-hydroxylase in the kidney, causing a decrease in 1,25-D3 synthesis.

In ADHR, as in XLH, abnormal laboratory findings are hypophosphatemia, an elevated alkaline phosphatase level, and a low or inappropriately normal 1,25-D3 level (see Table 51-4). Treatment is similar to the approach used in XLH.

**Autosomal Recessive Hypophosphatemic Rickets**

Autosomal recessive hypophosphatemic rickets (ARHR), type 1 is an extremely rare disorder caused by mutations in the gene encoding dentin matrix protein 1 (DMP1). ARHR, type 2 occurs in patients with mutations in the ENPP1 gene. Mutations in ENPP1 also cause generalized arterial calcification of infancy. Both types of ARHR are associated with elevated levels of FGF-23, leading to renal phosphate wasting, hypophosphatemia, and low or inappropriately normal levels of 1,25-D3. Treatment is similar to the approach used in XLH, although monitoring for arterial calcification is prudent in patients with ENPP1 mutations.

**Hereditary Hypophosphatemic Rickets with Hypercalciuria**

Hereditary hypophosphatemic rickets with hypercalciuria is a rare disorder that is mainly found in the Middle East.

**Pathophysiology**

This autosomal recessive disorder is caused by mutations in the gene for a sodium-phosphate cotransporter in the proximal tubule (SLC34A3). The renal phosphate leak causes hypophosphatemia, which then stimulates production of 1,25-D. The high level of 1,25-D increases intestinal absorption of calcium, suppressing PTH. Hypercalciuria ensues as a result of the high absorption of calcium and the low level of PTH, which normally decreases renal excretion of calcium.

**Clinical Manifestations**

The dominant symptoms are rachitic leg abnormalities (see Table 51-3), muscle weakness, and bone pain. Patients can have short stature, with a disproportionate decrease in the length of the lower extremities. The severity of the disease varies, and some family members have no evidence of rickets but have kidney stones secondary to hypercalciuria.

**Laboratory Findings**

Laboratory findings include hypophosphatemia, renal phosphate wasting, elevated serum alkaline phosphatase levels, and elevated 1,25-D3 levels. PTH levels are low (see Table 51-4).

**Treatment**

Therapy relies on oral phosphorus replacement (1-2.5 g/day of elemental phosphorus in 5 divided oral doses). Treatment of the hypophosphatemia decreases serum levels of 1,25-D3 and corrects the hypercalciuria. The response to therapy is usually excellent, with resolution of pain, weakness, and radiographic evidence of rickets.

**Overproduction of FGF-23**

Tumor-induced osteomalacia is more common in adults than in children, where it can produce classic rachitic findings. Most tumors are mesenchymal in origin and are usually benign, small, and located in bone. These tumors secrete FGF-23 and produce a biochemical phenotype that is similar to XLH, including urinary phosphate wasting, hypophosphatemia, elevated alkaline phosphatase levels, and low or inappropriately normal 1,25-D3 levels (see Table 51-4). Curative treatment is excision of the tumor. If the tumor cannot be removed, treatment is identical to that used for XLH.

Renal phosphate wasting leading to hypophosphatemia and rickets (or osteomalacia in adults) is a potential complication in McCune-Albright syndrome, an entity that includes the triad of polyostotic fibrous dysplasia, hyperpigmented macules, and polyendocrinopathy (see Chapter 563). Affected patients have inappropriately low levels of 1,25-D3 and elevated levels of alkaline phosphatase. The renal phosphate wasting and inhibition of 1,25-D3 synthesis are related to the polyostotic fibrous dysplasia. Patients have elevated levels of FGF-23, presumably produced by the dysplastic bone. Hypophosphatemic rickets can also occur in children with isolated polyostotic fibrous dysplasia. Although it is rarely possible, removal of the abnormal bone can cure this disorder in children with McCune-Albright syndrome. Most patients receive the same treatment as children with XLH. Bisphosphonate treatment decreases the pain and fracture risk associated with the bone lesions.

Rickets is an unusual complication of epidermal nevus syndrome (see Chapter 651). Patients have hypophosphatemic rickets due to renal phosphate wasting and also have an inappropriately normal or low level of 1,25-D as a consequence of excessive production of FGF-23. The timing of presentation with rickets varies from infancy to early adolescence. Resolution of hypophosphatemia and rickets has occurred after excision of the epidermal nevi in some patients, but not in others. In most cases, the skin lesions are too extensive to be removed, necessitating treatment with phosphorus supplements and 1,25-D3. Rickets caused by phosphate wasting is an extremely rare complication in children with neurofibromatosis (see Chapter 596).

**Fanconi Syndrome**

Fanconi syndrome is secondary to generalized dysfunction of the renal proximal tubule (see Chapter 529). There are renal losses of phosphate, amino acids, bicarbonate, glucose, urate, and other molecules that are normally reabsorbed in the proximal tubule. Some patients have partial dysfunction, with less generalized losses. The most clinically relevant consequences are hypophosphatemia caused by phosphate losses and proximal renal tubular acidosis caused by bicarbonate losses. Patients have rickets as a result of hypophosphatemia, with exacerbation from the chronic metabolic acidosis, which causes bone dissolution. Failure to thrive is a consequence of both rickets and renal tubular acidosis. Treatment is dictated by the etiology (see Chapter 529).

**Dent Disease (See Chapter 531.3)**

Dent disease is an X-linked disorder usually caused by mutations in the gene encoding a chloride channel that is expressed in the kidney (CLCN5). Some patients have mutations in the OCRL1 gene, which can also cause Lowe syndrome (see Chapter 530). Affected males have variable manifestations, including hematuria, nephrolithiasis, nephrocalcinosis, rickets, and chronic kidney disease. Almost all patients have low-molecular-weight proteinuria and hypercalciuria. Other, less universal abnormalities are aminoaciduria, glycosuria, hypophosphatemia, and hypokalemia. Rickets occurs in approximately 25% of patients, and it responds to oral phosphorus supplements. Some patients also need 1,25-D3, but this treatment should be used cautiously because it can worsen the hypercalciuria.

**Rickets of Prematurity** (See Chapter 106)

Rickets in very-low-birthweight infants has become a significant problem, as the survival rate for this group of infants has increased.

**Pathogenesis**

The transfer of calcium and phosphorus from mother to fetus occurs throughout pregnancy, but 80% occurs during the 3rd trimester. Premature birth interrupts this process, with rickets developing when the...
premature infant does not have an adequate supply of calcium and phosphorus to support mineralization of the growing skeleton.

Most cases of rickets of prematurity occur in infants with a birthweight <1,000 g. It is more likely to develop in infants with lower birthweight and younger gestational age. Rickets occurs because un-supplemented breast milk and standard infant formula do not contain enough calcium and phosphorus to supply the needs of the premature infant. Other risk factors include cholestatic jaundice, a complicated neonatal course, prolonged use of parenteral nutrition, the use of soy formula, and medications such as diuretics and corticosteroids.

**Clinical Manifestations**

Rickets of prematurity occurs 1-4 mo after birth. Infants can have nontraumatic fractures, especially of the legs, arms, and ribs. Most fractures are not suspected clinically. Because fractures and softening of the ribs lead to decreased chest compliance, some infants have respiratory distress due to atelectasis and poor ventilation. This rachitic respiratory distress usually develops >5 wk after birth, distinguishing it from the early-onset respiratory disease of premature infants. These infants have poor linear growth, with negative effects on growth persisting beyond 1 yr of age. An additional long-term effect is enamel hypoplasia. Poor bone mineralization can contribute to dolichocephaly. There may be classic rachitic findings, such as frontal bossing, rachitic rosary, craniotabes, and widened wrists and ankles (see Table 51-3). Most infants with rickets of prematurity have no clinical manifestations, and the diagnosis is based on radiographic and laboratory findings.

**Laboratory Findings**

Because of inadequate intake, the serum phosphorus level is low or low-normal in rickets of prematurity. The renal response is appropriate, with conservation of phosphate leading to a low urine phosphate level; the tubular reabsorption of phosphate is >95%. Most patients have normal levels of 25-D, unless there has been inadequate intake or poor absorption (discussed earlier). The hypophosphatemia stimulates renal 1α-hydroxylase, so levels of 1,25-D are high or high-normal. These high levels can contribute to bone demineralization, because 1,25-D stimulates bone resorption. Serum levels of calcium are low, normal, or high, and patients often have hypercalcemia. Elevated serum calcium levels and hypercalcemia are secondary to increased intestinal absorption and bone dissolution owing to elevation of 1,25-D levels and the inability to deposit calcium in bone because of an inadequate phosphate supply. The hypercalcemia indicates that phosphorus is the limiting nutrient for bone mineralization, although increased provision of phosphorus alone often cannot correct the mineralization defect; increased calcium is also necessary. Hence, there is an inadequate supply of calcium and phosphorus, but the deficiency in phosphorus is greater.

Alkaline phosphatase levels are often elevated, but some affected infants have normal levels. In some instances, normal alkaline phosphatase levels may be secondary to resolution of the bone demineralization because of an adequate mineral supply despite the continued presence of radiologic changes, which take longer to resolve. However, alkaline phosphatase levels may be normal despite active disease. No single blood test is 100% sensitive for the diagnosis of rickets. The diagnosis should be suspected in infants with an alkaline phosphatase level that is >5-6 times the upper limit of normal for adults (unless there is concomitant liver disease) or a phosphorus level <5.6 mg/dL. The diagnosis is confirmed by radiologic evidence of rickets, which is best seen on films of the wrists and ankles. Films of the arms and legs might reveal fractures. The rachitic rosary may be visible on chest x-ray. Unfortunately, x-rays cannot show early demineralization of bone because changes are not evident until there is >20-30% reduction in the bone mineral content.

**Diagnosis**

Because many premature infants have no overt clinical manifestations of rickets, screening tests are recommended. These tests should include weekly measurements of calcium, phosphorus, and alkaline phosphatase. Periodic measurement of the serum bicarbonate concentration is also important, because metabolic acidosis causes dissolution of bone. At least 1 screening x-ray for rickets at 6-8 wk of age is appropriate in infants who are at high risk for rickets; additional films may be indicated in very high risk infants.

**Prevention**

Provision of adequate amounts of calcium, phosphorus, and vitamin D significantly decreases the risk of rickets of prematurity. Parenteral nutrition is often necessary initially in very premature infants. In the past, adequate parenteral calcium and phosphorus delivery was difficult because of limits secondary to insolubility of these ions when their concentrations were increased. Current amino acid preparations allow higher concentrations of calcium and phosphate, decreasing the risk of rickets. Early transition to enteral feedings is also helpful. These infants should receive either human milk fortified with calcium and phosphorus or preterm infant formula, which has higher concentrations of calcium and phosphorus than standard formula. Soy formula should be avoided because there is decreased bioavailability of calcium and phosphorus. Increased mineral feedings should continue until the infant weighs 3-3.5 kg. These infants should also receive approximately 400 IU/day of vitamin D via formula and vitamin supplements.

**Treatment**

Therapy for rickets of prematurity focuses on ensuring adequate delivery of calcium, phosphorus, and vitamin D. If mineral delivery has been good and there is no evidence of healing, then it is important to screen for vitamin D deficiency by measuring serum 25-D. Measurement of PTH, 1,25-D, and urinary calcium and phosphorus may be helpful in some cases.

**DISTAL RENAL TUBULAR ACIDOSIS**

(See Chapter 530)

Distal renal tubular acidosis usually manifests with failure to thrive. Patients have a metabolic acidosis with an inability to acidify the urine appropriately. Hypercalcemia and nephrocalcinosis are typically present. There are many possible etiologies, including autosomal recessive and autosomal dominant forms. Rickets is variable, and it responds to alkali therapy (see Fig. 51-4).

**HYPERVITAMINOSIS D**

**Etiology**

Hypervitaminosis D is secondary to excessive intake of vitamin D. It can occur with long-term high intake or with a substantial, acute ingestion (see Table 51-1). Most cases are secondary to misuse of prescribed or nonprescription vitamin D supplements, but other cases have been secondary to accidental overfortification of milk, contamination of table sugar, and inadvertent use of vitamin D supplements as cooking oil. The recommended upper limits for long-term vitamin D intake are 1,000 IU for children <1 year old and 2,000 IU for older children and adults. Hypervitaminosis D can also result from excessive intake of synthetic vitamin D analogs (25-D, 1,25-D). Vitamin D intoxication is never secondary to excessive exposure to sunlight, probably because ultraviolet irradiation can transform vitamin D3 and its precursor into inactive metabolites.

**Pathogenesis**

Although vitamin D increases intestinal absorption of calcium, the dominant mechanism of the hypercalcemia is excessive bone resorption.

**Clinical Manifestations**

The signs and symptoms of vitamin D intoxication are secondary to hypercalcemia. GI manifestations include nausea, vomiting, poor feeding, constipation, abdominal pain, and pancreatitis. Possible cardiac findings are hypertension, decreased Q-T interval, and arrhythmias. The central nervous system effects of hypercalcemia include lethargy, hypotonia, confusion, disorientation, depression, psychosis, hallucinations, and coma. Hypercalcemia impairs renal concentrating
mechanisms, which can lead to polyuria, dehydration, and hypernatremia. Hypercalcemia can also lead to acute renal failure, nephrolithiasis, and nephrocalcinosis, which can result in chronic renal insufficiency. Deaths are usually associated with arrhythmias or dehydration.

**Laboratory Findings**
The classic findings in vitamin D intoxication are hypercalcemia and extremely elevated levels of 25-D (>150 ng/mL). Hyperphosphatemia is also common. PTH levels are appropriately decreased owing to hypercalcemia. Hypercalciuria is universally present and can lead to nephrocalcinosis, which is visible on renal ultrasound. Hypercalcemia and nephrocalcinosis can lead to renal insufficiency.

Surprisingly, levels of 1,25-D are usually normal. This may be a result of downregulation of renal 1α-hydroxylase by the combination of low PTH, hyperphosphatemia, and a direct effect of 1,25-D. There is evidence indicating that the level of free 1,25-D may be high, owing to displacement from vitamin D–binding proteins by 25-D. Nephrocalcinosis is often visible on ultrasound or CT scan. Anemia is sometimes present; the mechanism is unknown.

**Diagnosis and Differential Diagnosis**
The diagnosis is based on the presence of hypercalcemia and an elevated serum 25-D level, although children with excess intake of 1,25-D or another synthetic vitamin D preparation have normal levels of 25-D. With careful sleuthing, there is usually a history of excess intake of vitamin D, although in some situations (overfortification of milk by a dairy) the patient and family may be unaware.

The differential diagnosis of vitamin D intoxication focuses on other causes of hypercalcemia. Hyperparathyroidism produces hypophosphatemia, whereas vitamin D intoxication usually causes hyperphosphatemia. Williams syndrome is often suggested by phenotypic features and accompanying cardiac disease. Idiopathic infantile hypercalcemia occurs in children taking appropriate doses of vitamin D. Subcutaneous fat necrosis is a common cause of hypercalcemia in young infants; skin findings are usually present. The hypercalcemia of familial benign hypocalciuric hypercalcemia is mild, asymptomatic, and associated with hypocalciuria. Hypercalcemia of malignancy is an important consideration. High intake of calcium can also cause hypercalcemia, especially in the presence of renal insufficiency. Questioning about calcium intake should be part of the history in a patient with hypercalcemia. Occasionally, patients are intentionally taking high doses of calcium and vitamin D.

**Treatment**
The treatment of vitamin D intoxication focuses on control of hypercalcemia. Many patients with hypercalcemia are dehydrated as a result of polyuria from nephrogenic diabetes insipidus, poor oral intake, and vomiting. Rehydration lowers the serum calcium level via dilution and corrects prerenal azotemia. The resultant increased urine output increases urinary calcium excretion. Urinary calcium excretion is also increased by high urinary sodium excretion. The mainstay of the initial treatment is aggressive therapy with normal saline, often in conjunction with a loop diuretic to further increase calcium excretion.

Normal saline, with or without a loop diuretic, is often adequate for treating mild or moderate hypercalcemia. More significant hypercalcemia usually requires other therapies. Glucocorticoids decrease intestinal absorption of calcium by blocking the action of 1,25-D. There is also a decrease in the levels of 25-D and 1,25-D. The usual dosage of prednisone is 1-2 mg/kg/24 hr.

Calcitonin, which lowers calcium by inhibiting bone resorption, is a useful adjunct, but its effect is usually not dramatic. There is an excellent response to intravenous or oral bisphosphonates in vitamin D intoxication. Bisphosphonates inhibit bone resorption through their effects on osteoclasts. Hemodialysis using a low or 0 dialysate calcium can rapidly lower serum calcium in patients with severe hypercalcemia that is refractory to other measures.

Along with controlling hypercalcemia, it is imperative to eliminate the source of excess vitamin D. Additional sources of vitamin D such as multivitamins and fortified foods should be eliminated or reduced.

Avoidance of sun exposure, including the use of sunscreen, is prudent. The patient should also restrict calcium intake.

**Prognosis**
Most children make a full recovery, but hypervitaminosis D may be fatal or can lead to chronic kidney disease. Because vitamin D is stored in fat, levels can remain elevated for months, necessitating regular monitoring of 25-D, serum calcium, and urine calcium.

*Bibliography is available at Expert Consult.*
Chapter 51  Rickets and Hypervitaminosis D  341.e1

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Chapter 52

Vitamin E Deficiency

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Vitamin E is a fat-soluble vitamin and functions as an antioxidant, but its precise biochemical functions are not known. Vitamin E deficiency can cause hemolysis or neurologic manifestations and occurs in premature infants, in patients with malabsorption, and in an autosomal recessive disorder affecting vitamin E transport. Because of its role as an antioxidant, there is considerable research on the potential role of vitamin E supplementation in chronic illnesses.

PATHOGENESIS

The term vitamin E denotes a group of 8 compounds with similar structures and antioxidant activity. The most potent member of these compounds is α-tocopherol, which is also the main form in humans. The best dietary sources of vitamin E are vegetable oils, seeds, nuts, green leafy vegetables, and margarine (see Table 51-1).

The majority of vitamin E is located within cell membranes, where it prevents lipid peroxidation and the formation of free radicals. Other antioxidants, such as ascorbic acid, enhance the antioxidant activity of vitamin E. The importance of other functions of vitamin E is still being delineated.

Premature infants are particularly susceptible to vitamin E deficiency, because there is significant transfer of vitamin E during the last trimester of pregnancy. Vitamin E deficiency in premature infants causes thrombocytosis, edema, and hemolysis potentially causing anemia. The risk of symptomatic vitamin E deficiency was increased by the use of formulas for premature infants that had a high content of polyunsaturated fatty acids (PUFAs). These formulas led to a high content of PUFAs in red blood cell membranes, making them more susceptible to oxidative stress, which could be ameliorated by vitamin E. Oxidative stress was augmented by aggressive use of iron supplementation; iron increases the production of oxygen radicals. The incidence of hemolysis as a result of vitamin E deficiency in premature infants decreased secondary to the use of formulas with a lower content of PUFAs, less-aggressive use of iron, and provision of adequate vitamin E.

Because vitamin E is plentiful in common foods, primary dietary deficiency is rare except in premature infants and in severe, generalized malnutrition. Vitamin E deficiency does occur in children with fat malabsorption secondary to the need for bile acid for vitamin E absorption. Although symptomatic disease is most common in children with cholestatic liver disease, it can occur in patients with cystic fibrosis, celiac disease, short-bowel syndrome, or Crohn disease. The autosomal recessive disorder abetalipoproteinemia (see Chapter 86) causes fat malabsorption, and vitamin E deficiency is a common complication.
In **ataxia with isolated vitamin E deficiency** (AVED), a rare autosomal recessive disorder, there are mutations in the gene for α-tocopherol transfer protein (TTPA). Patients with this disorder are unable to incorporate vitamin E into lipoproteins before their release from the liver, leading to reduced serum levels of vitamin E. There is no associated fat malabsorption, and absorption of vitamin E from the intestine occurs normally.

**CLINICAL MANIFESTATIONS**

A severe, progressive neurologic disorder occurs in patients with prolonged vitamin E deficiency. Clinical manifestations do not appear until after 1 yr of age, even in children with cholestasis since birth. Patients may have cerebellar disease, posterior column dysfunction, and retinal disease. Loss of deep tendon reflexes is usually the initial finding. Subsequent manifestations include limb ataxia (intention tremor, dysdiadochokinesia), truncal ataxia (wide-based, unsteady gait), dysarthria, ophthalmoplegia (limited upward gaze), nystagmus, decreased proprioception (positive Romberg test), decreased vibratory sensation, and dysarthria. Some patients have pigmentary retinopathy. Visual field constriction can progress to blindness. Cognition and behavior can also be affected. Myopathy and cardiac arrhythmias are less-common findings.

In premature infants, hemolysis as a result of vitamin E deficiency typically develops during the 2nd mo of life. Edema may also be present.

**LABORATORY FINDINGS**

Serum vitamin E levels increase in the presence of high serum lipid levels, even when vitamin E deficiency is present. Hence, vitamin E status is best determined by measuring the ratio of vitamin E to serum lipids; a ratio <0.8 mg/g is abnormal in older children and adults; <0.6 mg/g is abnormal in infants <1 yr. Premature infants with hemolysis caused by vitamin E deficiency also often have elevated platelet counts.

Neurologic involvement can cause abnormal somatosensory evoked potentials and nerve conduction studies. Abnormalities on electroretinography can precede physical examination findings in patients with retinal involvement.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**

Premature infants with unexplained hemolytic anemia after the 1st mo of life, especially if thrombocytosis is present, either should be empirically treated with vitamin E or should have serum vitamin E and lipid levels measured. Children with neurologic findings and a disease that causes fat malabsorption should have their vitamin E status evaluated.

Because children with AVED do not have symptoms of malabsorption, a correct diagnosis requires a high index of suspicion. **Friedreich ataxia** has been misdiagnosed in some patients (see Chapter 597.1). Children with unexplained ataxia should be screened for vitamin E deficiency.

**TREATMENT**

For correction of deficiency in neonates, the dose of vitamin E is 25-50 units/day for 1 wk, followed by adequate dietary intake. Children with deficiency as a result of malabsorption should receive 1 unit/kg/day, with the dose adjusted based on levels; ongoing treatment is necessary. Children with AVED normalize their serum vitamin E levels with high doses of vitamin E and require ongoing treatment.

**PROGNOSIS**

The hemolytic anemia in infants resolves with correction of the vitamin E deficiency. Some neurologic manifestations of vitamin E deficiency may be reversible with early treatment, but many patients have little or no improvement. Importantly, treatment prevents progression.

**PREVENTION**

Premature infants should receive sufficient vitamin E via formula or breast milk fortifier and formula without a high content of PUFAs.
Bibliography


Chapter 53
Vitamin K Deficiency
Larry A. Greenbaum

Vitamin K is necessary for the synthesis of clotting factors II, VII, IX, and X; deficiency of vitamin K can result in clinically significant bleeding. Vitamin K deficiency typically affects infants, who experience a transient deficiency related to inadequate intake, or patients of any age who have decreased vitamin K absorption. Mild vitamin K deficiency can affect long-term bone and vascular health (see Chapters 103.4 and 480).

**PATHOGENESIS**

Vitamin K is a group of compounds that have a common naphthoquinone ring structure. Phylloquinone, called vitamin $K_1$, is present in a variety of dietary sources, with green leafy vegetables, liver, and certain legumes and plant oils having the highest content. Vitamin $K_1$ is the form used to fortify foods and as a medication in the United States. Vitamin $K_2$ is a group of compounds called menaquinones, which are produced by intestinal bacteria. There is uncertainty regarding the relative importance of intestinally produced vitamin $K_2$. Menaquinones are also present in meat, especially liver, and cheese. A menaquinone is used pharmacologically in some countries.

Vitamin K is a cofactor for $\gamma$-glutamyl carboxylase, an enzyme that performs posttranslational carboxylation, converting glutamate residues in proteins to $\gamma$-carboxyglutamate (Gla). The Gla residues, by facilitating calcium binding, are necessary for protein function.

The classic Gla-containing proteins involved in blood coagulation that are decreased in vitamin K deficiency are factors II (prothrombin), VII, IX, and X. Vitamin K deficiency causes a decrease in proteins C and S, which inhibit blood coagulation, and protein Z, which also has a role in coagulation. All of these proteins are made only in the liver, except for protein S, a product of various tissues.

Gla-containing proteins are also involved in bone biology (e.g., osteocalcin and protein S) and vascular biology (matrix Gla protein and protein S). Based on the presence of reduced levels of Gla, these proteins appear more sensitive than the coagulation proteins to subtle vitamin K deficiency. There is evidence suggesting that mild vitamin K deficiency might have a deleterious effect on long-term bone strength and vascular health.

Because it is fat soluble, vitamin K requires the presence of bile salts for its absorption. Unlike other fat-soluble vitamins, there are limited body stores of vitamin K. In addition, there is high turnover of vitamin K, and the vitamin $K$–dependent clotting factors have a short half-life. Hence, symptomatic vitamin K deficiency can develop within weeks when there is inadequate supply because of low intake or malabsorption.

There are 3 forms of vitamin K–deficiency bleeding (VKDB) of the newborn (see Chapter 103.4). Early VKDB was formerly called classic hemorrhagic disease of the newborn and occurs at 1-14 days of age. Early VKDB is secondary to low stores of vitamin K at birth as a result of the poor transfer of vitamin K across the placenta and inadequate intake during the 1st few days of life. In addition, there is no intestinal synthesis of vitamin $K_1$ because the newborn gut is sterile. Early VKDB
occurs mostly in breastfed infants as a consequence of the low vitamin K content of breast milk (formula is fortified). Delayed feeding is an additional risk factor.

Late VKDB most commonly occurs at 2-12 wk of age, although cases can occur up to 6 mo after birth. Almost all cases are in breastfed infants because of the low vitamin K content of breast milk. An additional risk factor is occult malabsorption of vitamin K, as occurs in children with undiagnosed cystic fibrosis or cholestatic liver disease (e.g., biliary atresia, α₁-antitrypsin deficiency). Without vitamin K prophylaxis, the incidence is 4-10/100,000 newborns.

The third form of VKDB of the newborn occurs at birth or shortly thereafter. It is secondary to maternal intake of medications (warfarin, phenobarbital, phenytol) that cross the placenta and interfere with vitamin K function.

VKDB as a result of fat malabsorption can occur in children of any age. Potential etiologies include cholestatic liver disease, pancreatic disease, and intestinal disorders (celiac sprue, inflammatory bowel disease, short-bowel syndrome). Prolonged diarrhea can cause vitamin K deficiency, especially in breastfed infants. Children with cystic fibrosis are most likely to have vitamin K deficiency if they have pancreatic insufficiency and liver disease.

Beyond infancy, low dietary intake by itself never causes vitamin K deficiency. However, the combination of poor intake and the use of broad-spectrum antibiotics that eliminate the intestine's vitamin K-producing bacteria can cause vitamin K deficiency. This scenario is especially common in the intensive care unit. Vitamin K deficiency can also occur in patients who receive total parenteral nutrition without vitamin K supplementation.

CLINICAL MANIFESTATIONS
In early VKDB, the most common sites of bleeding are the gastrointestinal (GI) tract, mucosal and cutaneous tissue, the umbilical stump, and the postcircumcision site; intracranial bleeding is less common. GI blood loss can be severe enough to require a transfusion. In contrast, the most common site of bleeding in late VKDB is intracranial, although cutaneous and GI bleeding may be the initial manifestation. Intracranial bleeding can cause convulsions, permanent neurologic sequelae, or death. In some cases of late VKDB, the presence of an underlying disorder may be suggested by jaundice or failure to thrive. Older children with vitamin K deficiency can present with bruising, mucocutaneous bleeding, or more serious bleeding.

LABORATORY FINDINGS
In patients with bleeding as a result of vitamin K deficiency, the prothrombin time (PT) is prolonged. The PT must be interpreted based on the patient's age, because it is normally prolonged in newborns (see Chapter 476). The partial thromboplastin time is usually prolonged, but it may be normal in early deficiency; factor VII has the shortest half-life of the coagulation factors and is the first to be affected by vitamin K deficiency, but isolated factor VII deficiency does not affect the partial thromboplastin time. The platelet count and fibrinogen level are normal.

When there is mild vitamin K deficiency, the PT is normal, but there are elevated levels of the undercarboxylated forms of the proteins that are normally carboxylated in the presence of vitamin K. These undercarboxylated proteins are called proteins induced by vitamin K absence (PIVKA). Measurement of undercarboxylated factor II (PIVKA-II) can be used to detect mild vitamin K deficiency. Determination of blood vitamin K levels is less useful because of significant variation based on recent dietary intake; levels do not always reflect tissue stores.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS
The diagnosis is established by the presence of a prolonged PT that corrects rapidly after administration of vitamin K, which stops the active bleeding. Other possible causes of bleeding and a prolonged PT include disseminated intravascular coagulation (DIC), liver failure, and rare hereditary deficiencies of clotting factors. DIC, which is most commonly secondary to sepsis, is associated with thrombocytopenia, low fibrinogen, and elevated D-dimers. Most patients with DIC have hemodynamic instability that does not correct with restoration of blood volume. Severe liver disease results in decreased production of clotting factors; the PT does not fully correct with administration of vitamin K. Children with a hereditary disorder have a deficiency in a specific clotting factor (I, II, V, VII, X).

Coumarin derivatives inhibit the action of vitamin K by preventing its recycling to an active form after it functions as a cofactor for γ-glutamyl carboxylase. Bleeding can occur with overdosage of the commonly used anticoagulant warfarin or with ingestion of rodent poison, which contains a coumarin derivative. High doses of salicylates also inhibit vitamin K activity, potentially leading to a prolonged PT and clinical bleeding.

TREATMENT
Infants with VKDB should receive 1 mg of parenteral vitamin K. The PT should decrease within 6 hr and normalize within 24 hr. For rapid correction in adolescents, the parenteral dose is 2.5-10 mg. In addition to vitamin K, a patient with severe, life-threatening bleeding should receive an infusion of fresh-frozen plasma, which corrects the coagulopathy rapidly. Children with vitamin K deficiency as a consequence of malabsorption require chronic administration of high doses of oral vitamin K (2.5 mg twice/wk to 5 mg/day). Parenteral vitamin K may be necessary if oral vitamin K is ineffective.

PREVENTION
Administration of either oral or parenteral vitamin K soon after birth prevents early VKDB of the newborn. In contrast, a single dose of oral vitamin K does not prevent a substantial number of cases of late VKDB. However, a single intramuscular injection of vitamin K (1 mg), the current practice in the United States, is almost universally effective, except in children with severe malabsorption. This increased efficacy of the intramuscular form is thought to be the result of a depot effect. Concerns about an association between parenteral vitamin K at birth and the later development of malignancy are unsubstantiated.

Discontinuing the offending medications before delivery can prevent VKDB attributable to maternal medications. If this is not possible, administration of vitamin K to the mother may be helpful. In addition, the neonate should receive parenteral vitamin K immediately after birth. If parenteral vitamin K does not correct the coagulopathy rapidly, then the child should receive fresh frozen plasma.

Children who are at high risk for malabsorption of vitamin K should receive supplemental vitamin K and periodic measurement of the PT.

Bibliography is available at Expert Consult.
Bibliography
Micronutrients include vitamins (see Chapters 48-53) and trace elements. By definition, a trace element is <0.01% of the body weight. Trace elements have a variety of essential functions (Table 54-1). With the exception of iron deficiency, trace element deficiency (see Table 54-1) is uncommon in developed countries, but some deficiencies (iodine, zinc, selenium) are important public health problems in a number of developing countries. Because of low nutritional requirements and plentiful supply, deficiencies of some of the trace elements are extremely rare in humans and typically occur in patients receiving
unusual diets or prolonged total parenteral nutrition without adequate delivery of a specific trace element. They can also occur in children with short bowel or malabsorption. Excess intake of trace elements (see Table 54-1) is uncommon, but it can result from environmental exposure or overuse of supplements.

For a number of reasons, children are especially susceptible to trace element deficiency. First, growth creates an increased demand for most trace elements. Second, some organs are more likely to sustain permanent damage because of trace element deficiency during childhood. The developing brain is particularly vulnerable to the consequences of certain deficiency states (iron, iodide). Similarly, adequate fluoride is most critical for dental health during childhood. Third, as children in the developing world, are more prone to gastrointestinal disorders that can cause trace element deficiencies because of malabsorption.

A normal diet provides adequate intake of most trace elements. However, the intake of certain trace elements varies significantly in different geographic locations. Iodide-containing food is plentiful near the ocean, but inland areas often have inadequate sources, leading to goiter and hypothyroidism. Iodine deficiency is not a problem in the United States because of the widespread use of iodized salt; however, symptomatic iodine deficiency (goiter and hypothyroidism) is common in many developing countries. Selenium content of the soil and consequently of food is also quite variable. Dietary selenium deficiency (associated with cardiomyopathy) occurs in certain locations, such as some parts of China.

The consequences of severe isolated trace mineral deficiency are illustrated in certain genetic disorders. The manifestations of Menkes disease (see Chapters 357.5 and 599) are caused by a mutation in the gene coding for a protein that facilitates intestinal copper absorption. This mutation results in severe copper deficiency; subcutaneous copper is an effective treatment. The recessive disorder acrodermatitis enteropathica (see Chapter 671) is secondary to malabsorption of zinc. These patients respond dramatically to zinc supplementation.

Children can have apparently asymptomatic deficiencies of certain trace elements but still benefit from supplementation. As an example, zinc is highly effective in treating children before or during diarrheal illnesses in the developing world.

### Table 54-1: Trace Elements

<table>
<thead>
<tr>
<th>ELEMENT</th>
<th>PHYSIOLOGY</th>
<th>EFFECTS OF DEFICIENCY</th>
<th>EFFECTS OF EXCESS</th>
<th>DIETARY SOURCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromium</td>
<td>Potentiates the action of insulin</td>
<td>Impaired glucose tolerance, peripheral neuropathy, and encephalopathy</td>
<td>Unknown</td>
<td>Meat, grains, fruits, and vegetables</td>
</tr>
<tr>
<td>Copper</td>
<td>Absorbed via specific intestinal transporter</td>
<td>Microcytic anemia, osteoporosis, neutropenia, neurologic symptoms, depigmentation of hair and skin</td>
<td>Acute: nausea, emesis, abdominal pain, coma, and hepatic necrosis</td>
<td>Vegetables, grains, nuts, liver, margarine, legumes, corn oil</td>
</tr>
<tr>
<td>Fluoride</td>
<td>Incorporated into bone</td>
<td>Dental caries (see Chapter 312)</td>
<td>Chronic: dental fluorosis</td>
<td>Toothpaste, fluoridated water</td>
</tr>
<tr>
<td>Iodine</td>
<td>Component of thyroid hormone (see Chapter 564)</td>
<td>Hypothyroidism (see Chapters 566 and 568)</td>
<td>Hypothyroidism and goiter (see Chapters 566 and 568); maternal excess can cause congenital hypothyroidism and goiter (see Chapter 568.1)</td>
<td>Saltwater fish, iodized salt</td>
</tr>
<tr>
<td>Iron</td>
<td>Component of hemoglobin, myoglobin, cytochromes, and other enzymes</td>
<td>Anemia (see Chapter 456), decreased alertness, impaired learning</td>
<td>Acute (see Chapter 63): nausea, vomiting, diarrhea, abdominal pain, and hypotension</td>
<td>Meat, fortified foods</td>
</tr>
<tr>
<td>Manganese</td>
<td>Enzyme cofactor</td>
<td>Hypercholesterolemia, weight loss, decreased clotting proteins*</td>
<td>Neurologic manifestations, cholestatic jaundice</td>
<td>Nuts, meat, grains, tea</td>
</tr>
<tr>
<td>Molybdenum</td>
<td>Enzyme cofactor (xanthine oxidase and others)</td>
<td>Tachycardia, tachypnea, night blindness, irritability, coma*</td>
<td>Hyperuricemia and increased risk of gout</td>
<td>Legumes, grains, liver</td>
</tr>
<tr>
<td>Selenium</td>
<td>Enzyme cofactor (prevents oxidative damage)</td>
<td>Cardiomyopathy (Keshan disease), myopathy</td>
<td>Nausea, diarrhea, neurologic manifestations, nail and hair changes, garlic odor</td>
<td>Meat, seafood, whole grains, garlic</td>
</tr>
<tr>
<td>Zinc</td>
<td>Constituent of zinc-finger proteins, which regulate gene transcription</td>
<td>Decreased growth, dermatitis of extremities and around orifices, impaired immunity, poor wound healing, hypogonadism, diarrhea</td>
<td>Abdominal pain, diarrhea, vomiting</td>
<td>Meat, shellfish, whole grains, legumes, cheese</td>
</tr>
</tbody>
</table>

*These deficiency states have been reported only in case reports associated with parenteral nutrition or highly unusual diets.
Zinc deficiency is quite common in the developing world and is often associated with malnutrition or other micronutrient deficiencies (iron). Chronic zinc deficiency is associated with dwarfism, hypogonadism, dermatitis, and T-cell immunodeficiency. Diets rich in phytates bind zinc, impairing its absorption. Zinc supplementation in at-risk children reduces the incidence and severity of diarrhea, pneumonia, and possibly malaria. In developing countries, children who have diarrhea may benefit from zinc supplementation, especially if there is underlying malnutrition.

*Bibliography is available at Expert Consult.*
Bibliography


Chapter 55
Electrolyte and Acid-Base Disorders

55.1 Composition of Body Fluids
Larry A. Greenbaum

TOTAL BODY WATER
Total body water (TBW) as a percentage of body weight varies with age (Fig. 55-1). The fetus has very high TBW, which gradually decreases to approximately 75% of birthweight for a term infant. Premature infants have higher TBW than term infants. During the 1st yr of life, TBW decreases to approximately 60% of body weight and basically remains at this level until puberty. At puberty, the fat content of females increases more than that in males, who acquire more muscle mass than females. Because fat has very low water content and muscle has high water content, by the end of puberty TBW in males remains at 60%, but TBW in females decreases to approximately 50% of body weight. The high fat content in overweight children causes a decrease in TBW as a percentage of body weight. During dehydration, TBW decreases and, thus, is a smaller percentage of body weight.

FLUID COMPARTMENTS
TBW is divided between 2 main compartments: intracellular fluid (ICF) and extracellular fluid (ECF). In the fetus and newborn, the ECF volume is larger than the ICF volume (see Fig. 55-1). The normal postnatal diuresis causes an immediate decrease in the ECF volume. This is followed by continued expansion of the ICF volume, which results from cellular growth. By 1 yr of age, the ratio of the ICF volume to the ECF volume approaches adult levels. The ECF volume is approximately 20-25% of body weight, and the ICF volume is approximately 30-40% of body weight, close to twice the ECF volume (Fig. 55-2). With puberty, the increased muscle mass of males causes them to have a higher ICF volume than females. There is no significant difference in the ECF volume between postpubertal females and males.

The ECF is further divided into the plasma water and the interstitial fluid (see Fig. 55-2). The plasma water is 5% of body weight. The blood volume, given a hematocrit of 40%, is usually 8% of body weight, although it is higher in newborns and young infants; in premature newborns, it is approximately 10% of body weight. The volume of plasma water can be altered by pathologic conditions, including dehydration, anemia, polythemia, heart failure, abnormal plasma osmolality, and hypoalbuminemia. The interstitial fluid, normally 15% of body weight, can increase dramatically in diseases associated with edema, such as heart failure, protein-losing enteropathy, liver failure, nephrotic syndrome, and sepsis. An increase in interstitial fluid also occurs in patients with ascites or pleural effusions.

There is a delicate equilibrium between the intravascular fluid and the interstitial fluid. The balance between hydrostatic and oncotic forces regulates the intravascular volume, which is critical for proper tissue perfusion. The intravascular fluid has a higher concentration of albumin than the interstitial fluid, and the consequent oncotic force draws water into the intravascular space. The maintenance of this gradient depends on the limited permeability of albumin across the capillaries. The hydrostatic pressure of the intravascular space, which is due to the pumping action of the heart, drives fluid out of the intravascular space. These forces favor movement into the interstitial space at the arterial ends of the capillaries. The decreased hydrostatic forces and increased oncotic forces, which result from the dilutional increase in albumin concentration, cause movement of fluid into the venous ends of the capillaries. Overall, there is usually a net movement of fluid out of the intravascular space to the interstitial space, but this fluid is returned to the circulation via the lymphatics. An imbalance in these forces may cause expansion of the interstitial volume at the expense of the intravascular volume. In children with hypoalbuminemia, the decreased oncotic pressure of the intravascular fluid contributes to the development of edema. Loss of fluid from the intravascular space may compromise the intravascular volume, placing the child at risk for inadequate blood flow to vital organs. This is especially likely in diseases in which capillary leak occurs because the loss of albumin from the intravascular space is associated with an increase in the albumin concentration in the interstitial space, further compromising the oncotic forces that normally maintain intravascular volume. In contrast, with heart failure, there is an increase in venous hydrostatic pressure from expansion of the intravascular volume, which is caused by impaired pumping by the heart, and the increase in venous pressure causes fluid to move from the intravascular space to the interstitial space. Expansion of the intravascular volume and increased intravascular pressure also cause the edema that occurs with acute glomerulonephritis.

ELECTROLYTE COMPOSITION
The composition of the solutes in the ICF and ECF are very different (Fig. 55-3). Sodium and chloride are the dominant cation and anion, respectively, in the ECF. The sodium and chloride concentrations in the ICF are much lower. Potassium is the most abundant cation in the ICF, and its concentration within the cells is approximately 30 times higher than in the ECF. Proteins, organic anions, and phosphate are the most plentiful anions in the ICF. The dissimilarity between the anions in the ICF and the ECF is largely determined by the presence of intracellular molecules that do not cross the cell membrane, the barrier separating the ECF and the ICF. In contrast, the difference in the distribution of cations—sodium and potassium—is a result of the activity of the Na⁺,K⁺-adenosine triphosphatase (ATPase) pump, which uses cellular energy to actively extrude sodium from cells and move potassium into cells. The chemical gradient between the intracellular potassium concentration and the extracellular potassium concentration creates the electrical gradient across the cell membrane. The concentration-dependent movement of potassium out of the cell makes the intracellular space negative relative to the extracellular space.

The difference in the electrolyte compositions of the ECF and the ICF has important ramifications in the evaluation and treatment of electrolyte disorders. The serum concentration of an electrolyte, which is measured clinically, does not always reflect the body content. This is because of the larger volume of the ICF compared with the ECF and the variation in electrolyte concentrations between these 2 compartments. The intracellular potassium concentration is much higher than the serum concentration. A shift of potassium from the intracellular space can maintain a normal or even an elevated serum potassium concentration, despite massive losses of potassium from the intracellular space. This is dramatically seen in diabetic ketoacidosis, in which a state of significant potassium depletion is often masked because of a transmembrane shift of potassium from the ICF to the ECF. For potassium and phosphorus, electrolytes with a high intracellular concentration, the serum level may not reflect total body content. Similarly, the serum calcium concentration does not predict the body content of calcium, which is largely in bone.
Electrolyte and Acid-Base Disorders

Chapter 55

Electrolyte and Acid-Base Disorders

Osmolality

The ICF and the ECF are in osmotic equilibrium because the cell membrane is permeable to water. If the osmolality in 1 compartment changes, then water movement leads to a rapid equalization of osmolality. This can lead to significant shifts of water between the intracellular space and the extracellular space. Clinically, the primary process is usually a change in the osmolality of the ECF, with a resultant shift of water into the ICF if the ECF osmolality decreases or a shift of water out of the ICF if the ECF osmolality increases. The osmolality of the ECF can be determined, and it usually equals the ICF osmolality. The plasma osmolality is normally 285-295 mOsm/kg, and it is measured by the degree of freezing point depression. The plasma osmolality can also be estimated by a calculation based on the following formula:

\[ \text{Osmolality} = \frac{2 \times [\text{Na}] + [\text{glucose}]}{18} + \frac{[\text{BUN}]}{2.8} \]

Glucose and blood urea nitrogen (BUN) are measured in mg/dL. Division of these values by 18 and 2.8, respectively, as shown, converts the units into mmol/L. Multiplication of the sodium value by 2 accounts for its accompanying anions, principally chloride and bicarbonate. The calculated osmolality is usually slightly lower than the measured osmolality.

Glucose and urea normally contribute little to the plasma osmolality; multiplication of the sodium value by 2 provides an approximation of the osmolality. Urea is not confined to the extracellular space because it readily crosses the cell membrane and its intracellular concentration approximately equals its extracellular concentration. Whereas an elevated sodium concentration causes a shift of water from the intracellular space, with uremia, there is no osmolar gradient between the 2 compartments and, consequently, no movement of water. The only exception is during hemodialysis, when the decrease in extracellular urea is so rapid that the intracellular urea does not have time to equilibrate. This may lead to the disequilibrium syndrome, in which water shifts into brain cells, potentially causing severe symptoms. Ethanol, because it freely crosses cell membranes, is another ineffective osmole. The effective osmolality can be calculated as follows:

\[ \text{Effective osmolality} = 2 \times [\text{Na}] + [\text{glucose}] / 18 \]

The effective osmolality (also called the tonicity) determines the osmotic force that is mediating the shift of water between the ECF and the ICF.

Hyperglycemia causes an increase in the plasma osmolality because it is not in equilibrium with the intracellular space. During hyperglycemia there is a shift of water from the intracellular space to the extracellular space. This is clinically important in children with hyperglycemia during diabetic ketoacidosis. The shift of water causes dilution of the sodium in the extracellular space, causing hyponatremia despite an elevated plasma osmolality. The magnitude of this effect can be calculated as follows:

\[ [\text{Na}]_{\text{corrected}} = [\text{Na}]_{\text{measured}} + 1.6 \times ([\text{glucose}] - 100 \text{ mg/dL}) / 100 \]

where \([\text{Na}]_{\text{measured}}\) is sodium concentration measured by the clinical laboratory and \([\text{Na}]_{\text{corrected}}\) is corrected sodium concentration (the
sodium concentration if the glucose concentration were normal and its accompanying water moved back into the cells). The $[\text{Na}]_{\text{corrected}}$ is the more reliable indicator of the patient’s true ratio of total body sodium to TBW, the normal determinant of the sodium concentration.

Normally, the measured osmolality and the calculated osmolality are within 10 mOsm/kg. However, there are some clinical situations in which this does not occur. The presence of unmeasured osmolytes causes the measured osmolality to be significantly elevated in comparison with the calculated osmolality. This difference is the osmolar gap, which is present when the measured osmolality exceeds the calculated osmolality by >10 mOsm/kg. Examples of unmeasured osmolytes include ethanol, ethylene glycol, methanol, sucrose, sorbitol, and mannitol. These substances increase the measured osmolality but are not part of the equation for calculating osmolality. The presence of an osmolar gap is a clinical clue to the presence of unmeasured osmolytes and may be diagnostically useful when there is clinical suspicion of poisoning with methanol or ethylene glycol.

**Pseudohyponatremia** is a second situation in which there is discordance between the measured osmolality and the calculated osmolality. Lipids and proteins are the solids of the serum. In patients with elevated serum lipids or proteins, the water content of the serum decreases because water is displaced by the larger amount of solids. Some instruments measure sodium concentration by determining the amount of sodium per liter of serum, including the solid component. When the solid component increases, there is a decrease in the sodium concentration per liter of serum, despite a normal concentration of sodium when based on the amount of sodium per liter of serum water. It is the concentration of sodium in serum water that is physiologically relevant. A similar problem occurs when using instruments that require dilution of the sample prior to measurement of sodium (indirect potentiometry). In both situations, the plasma osmolality is normal despite the presence of pseudohyponatremia, because the method for measuring osmolality is not appreciably influenced by the percentage of serum that is composed of lipids and proteins. Pseudohyponatremia is diagnosed by the finding of a normal measured plasma osmolality despite hyponatremia. This laboratory artifact does not occur if the sodium concentration in water is measured directly with an ion-specific electrode, such as occurs with the instruments used for measuring arterial blood gases. **Pseudohypernatremia** may occur in patients with very low levels of serum proteins via a similar mechanism.

When there are no unmeasured osmolytes and pseudohyponatremia is not a concern, the calculated osmolality provides an accurate estimate of the plasma osmolality. Measurement of plasma osmolality is useful for detecting or monitoring unmeasured osmolytes and confirming the presence of true hyponatremia. Whereas many children with high plasma osmolality are dehydrated—as seen with hypernatremic dehydration or diabetic ketoacidosis—high osmolality does not always equate with dehydration. A child with *salt poisoning* or *uremia* has an elevated plasma osmolality but may be volume overloaded. In many situations, it is best to focus on the components of the plasma osmolality and to analyze them individually to reach a correct clinical conclusion.

* Bibliography is available at Expert Consult.

## 55.2 Regulation of Osmolality and Volume

_Larry A. Greenbaum_

The regulation of plasma osmolality and the intravascular volume is controlled by independent systems for water balance, which determines osmolality, and sodium balance, which determines volume status. Maintenance of normal osmolality depends on control of water balance. Control of volume status depends on regulation of sodium balance. When volume depletion is present, it takes precedence over regulation of osmolality, and retention of water contributes to the maintenance of intravascular volume.

### REGULATION OF OSMOLALITY

The plasma osmolality is tightly regulated and maintained at 285-295 mOsm/kg. Modification of water intake and excretion maintains normal plasma osmolality. In the steady state, the combination of water intake and water produced by the body from oxidation balances water losses from the skin, lungs, urine, and gastrointestinal tract. Only water intake and urinary losses can be regulated.

Osmoreceptors in the hypothalamus sense the plasma osmolality (see Chapter 556). An elevated effective osmolality leads to secretion of antidiuretic hormone (ADH) by neurons in the supraoptic and paraventricular nuclei in the hypothalamus. The axons of these neurons terminate in the posterior pituitary. Circulating ADH binds to its V2 receptors in the collecting duct cells of the kidney, and, via the generation of cyclic adenosine monophosphate, causes insertion of water channels (aquaporin-2) into the renal collecting ducts. This produces increased permeability to water, permitting resorption of water into the hypertonic renal medulla. The end result is that the urine concentration increases and water excretion decreases. Urinary water losses cannot be completely eliminated because there is obligatory excretion of urinary solutes, such as urea and sodium. The regulation of ADH secretion is tightly linked to plasma osmolality, responses being detectable with a 1% change in the osmolality. ADH secretion virtually disappears when the plasma osmolality is low, allowing excretion of maximally dilute urine. The consequent loss of free water (water without sodium) corrects the plasma osmolality. ADH secretion is not an all-or-nothing response; there is a graded adjustment as the osmolality changes.

Production of concentrated urine under the control of ADH requires a hypertonic renal medulla. The countercurrent multiplier, produced by the loop of Henle and the vasa recta, generates this hypertonicity. ADH stimulates sodium transport in the loop of Henle, helping to maintain this gradient when water retention is necessary.

Water intake is regulated by hypothalamic osmoreceptors, although these are different from the osmoreceptors that determine ADH secretion. These hypothalamic osmoreceptors, by linking to the cerebral cortex, stimulate thirst when the serum osmolality increases. Thirst occurs with a small increase in the serum osmolality.

**Control of osmolality is subordinate to maintenance of an adequate intravascular volume.** When volume depletion is present, both ADH secretion and thirst are stimulated, regardless of the plasma osmolality. The sensation of thirst requires moderate volume depletion but only a 1-2% change in the plasma osmolality. Although all of the mechanisms are not clear, angiotensin II, which is increased during volume depletion, is known to stimulate thirst. Baroreceptors, when sensing volume depletion, may also stimulate thirst.

A number of conditions can limit the kidney’s ability to excrete adequate water to correct low plasma osmolality. In the **syndrome of inappropriate antidiuretic hormone (SIADH)**, ADH continues to be produced despite a low plasma osmolality. In the presence of ADH, urinary dilution does not occur, and sufficient water is not excreted (see Chapters 55.5 and 559).

The glomerular filtration rate (GFR) affects the kidney’s ability to eliminate water. With a decrease in the GFR, less water is delivered to the collecting duct, limiting the amount of water that can be excreted. The impairment in the GFR must be quite significant to limit the kidney’s ability to respond to an excess of water.

The **minimum urine osmolality** is approximately 30-50 mOsm/kg. This places an upper limit on the kidney’s ability to excrete water; sufficient solute must be present to permit water loss. Massive water intoxication may exceed this limit, whereas a lesser amount of water is necessary in the child with a diet that has very little solute. This is occasionally seen and can produce severe hyponatremia in children who receive little salt and have little urea production as a result of inadequate protein intake. Volume depletion is an extremely important cause of decreased water loss by the kidney despite a low plasma osmolality. This “appropriate” secretion of ADH occurs because volume depletion takes precedence over the osmolality in the regulation of ADH.

The normal response to increased plasma osmolality is conservation of water by the kidney. In **central diabetes insipidus**, this does not
Bibliography


occurs because of an absence of ADH secretion (see Chapters 55.3 and 558). Patients with *nephrogenic diabetes insipidus* have an inability to respond to ADH and produce dilute urine despite an increase in plasma osmolality (see Chapters 55.3 and 530).

The **maximum urine osmolality** is approximately 1,200 mOsm/kg. The obligatory solute losses dictate the minimum volume of urine that must be produced, even when maximally concentrated. Obligatory water losses increase in patients with high salt intake or high urea losses, as may occur after relief of a urinary obstruction or during recovery from acute tubular necrosis. An increase in urinary solute and, consequently, water losses occurs with an **osmotic diuresis**, which occurs classically from glycosuria in diabetes mellitus as well as iatrogenically after mannitol administration. There are developmental changes in the kidney's ability to concentrate the urine. The maximum urine osmolality in a newborn, especially a premature newborn, is less than that in an older infant or child. This limits the ability to conserve water and makes such a patient more vulnerable to hypernephremic dehydration. Very high fluid intake, as seen with **psychogenic polydipsia**, can dilute the high osmolality in the renal medulla, which is necessary for maximal urinary concentration. If fluid intake is restricted in patients with this condition, there may be some impairment in the kidney's ability to concentrate the urine, although this defect corrects after a few days without polydipsia. This may also occur during the initial treatment of central diabetes insipidus with desmopressin acetate; the renal medulla takes time to achieve its normal maximum osmolality. Loop diuretics, such as furosemide, by inhibiting sodium resorption in the ascending limb of the loop of Henle, decrease medullary hypertonicity, preventing excretion of maximally concentrated urine.

**REGULATION OF VOLUME**

An appropriate intravascular volume is critical for survival; both volume depletion and volume overload may cause significant morbidity and mortality. Because sodium is the principal extracellular cation and it is restricted to the ECF, adequate body sodium is necessary for maintenance of intravascular volume. The principal extracellular anion, chloride, is also necessary, but for simplicity, sodium balance is considered the main regulator of volume status because body content of sodium and that of chloride usually change proportionally, given the need for equal numbers of cations and anions. In some situations, chloride depletion is considered the dominant derangement causing volume depletion (metabolic alkalosis with volume depletion). In other situations, such as volume depletion with metabolic acidosis, sodium depletion may exceed chloride depletion.

The kidney determines sodium balance because there is little homeostatic control of sodium intake, even though salt craving does occasionally occur, typically in children with chronic renal salt loss. The kidney regulates sodium balance by altering the percentage of filtered sodium that is resorbed along the nephron. Normally, the kidney excretes <1% of the sodium filtered at the glomerulus. In the absence of disease, extrarenal losses and urinary output match intake, with the kidney having the capacity to adapt to large variations in sodium intake. When necessary, urinary sodium excretion can be reduced to virtually undetectable levels or increased dramatically.

Urinary sodium excretion is regulated by both intrarenal and extra-renal mechanisms. The most important determinant of renal sodium excretion is the volume status of the child; it is the effective intravascular volume that influences urinary sodium excretion. The effective intravascular volume is the volume status that is sensed by the body's regulatory mechanisms. Heart failure is a state of volume overload, but the effective intravascular volume is low because poor cardiac function prevents adequate perfusion of the kidneys and other organs. This fact explains the avid renal sodium retention that is often present in patients with heart failure.

Sodium resorption occurs throughout the nephron. Whereas the majority of filtered sodium is resorbed in the proximal tubule and the loop of Henle, the distal tubule and the collecting duct are the main sites for precise regulation of sodium balance. Approximately 65% of the filtered sodium is reclaimed in the proximal tubule, which is the major site for resorption of bicarbonate, glucose, phosphate, amino acids, and other substances that are filtered by the glomerulus. The transport of all these substances is linked to sodium resorption by cotransporters, or a sodium-hydrogen exchanger in the case of bicarbonate. This link is clinically important for bicarbonate and phosphate because their resorption parallels sodium resorption. In patients with **metabolic alkalosis and volume depletion**, correction of the metabolic alkalosis requires urinary loss of bicarbonate, but the volume depletion stimulates sodium and bicarbonate retention, preventing correction of the alkalosis. Volume expansion causes increased urinary losses of phosphate, even when there is phosphate depletion. Resorption of uric acid and urea occurs in the proximal tubule and increases when sodium retention increases. This arrangement accounts for the elevated uric acid and BUN measurements that often accompany dehydration, which is a stimulus for sodium retention in the proximal tubule. The cells of the proximal tubule are permeable to water; thus, water resorption in this segment parallels sodium resorption.

The loop of Henle is, in terms of absolute amount, the second most important site of sodium resorption along the nephron. The Na⁺,K⁺,2Cl⁻ cotransporter on the luminal side of the membrane reclaims filtered sodium and chloride, whereas most of the potassium is recycled back into the lumen. This is the transporter that is inhibited by furosemide and other loop diuretics, which are highly effective at increasing sodium excretion. The ascending limb of the loop of Henle is not permeable to water, permitting sodium retention without water. ADH stimulates sodium retention in this segment; this arrangement helps create a more hypertonic medulla, which maximizes water conservation when ADH acts in the medullary collecting duct. Because loop diuretics inhibit sodium retention in this segment, their use causes a less hypertonic medulla, permitting excretion of maximally concentrated urine in the presence of ADH.

Sodium retention in the distal tubule is mediated by the thiazide-sensitive Na⁺,Cl⁻ cotransporter. This segment of the nephron is relatively impermeable to water, and along with sodium and chloride retention, the distal tubule is important for delivery of fluid with a low sodium concentration to the collecting duct. This allows for excretion of water without sodium in patients who stop secreting ADH because of low plasma osmolality. Thiazide diuretics, by inhibiting sodium and chloride retention in this segment, prevent the excretion of water without electrolytes—partially explaining the severe hyponatremia that occasionally develops in patients receiving chronic thiazide diuretics.

The collecting duct, the final segment of the nephron, is important for the regulation of excretion of water, potassium, acid, and sodium. Even though the amount of sodium resorbed in this segment is less than in any other segment, this is the critical site for the regulation of sodium balance. Sodium resorption occurs via a sodium channel that is regulated by aldosterone. When these channels are open under the influence of aldosterone, almost all of the sodium can be resorbed. The uptake of sodium creates a negative charge in the lumen of the collecting duct, which facilitates the secretion of potassium and hydrogen ions. The potassium-sparing diuretics amiloride and triamterene block these sodium channels, and the inhibition of sodium uptake decreases potassium excretion. The potassium-sparing diuretic spironolactone blocks the binding of aldosterone to its receptor; thus, it indirectly decreases the activity of the sodium channels. The collecting duct is important for the regulation of water balance because it responds to ADH by inserting water channels that increase the permeability to water, and the hypertonicity of the renal medulla allows for maximal concentration of the urine.

The amount of sodium filtered at the glomerulus is directly proportional to the GFR. If sodium resorption in the nephron were constant, complete resorption of sodium with a small decrease in the GFR and significant renal sodium wasting with a small increase would result. This does not occur; however, because sodium resorption in the nephron is proportional to sodium delivery, a principle called *glomerular tubular balance*.

The renin-angiotensin system is an important regulator of renal sodium excretion. The juxtaglomerular apparatus produces renin in
response to decreased effective intravascular volume. Specific stimuli for renin release are decreased perfusion pressure in the afferent arteriole of the glomerulus, decreased delivery of sodium to the distal nephron, and β–adrenergic agonists, which increase in response to intravascular volume depletion. Renin, a proteolytic enzyme, cleaves angiotensinogen, producing angiotensin I. Angiotensin-converting enzyme converts angiotensin I into angiotensin II. The actions of angiotensin II include direct stimulation of the proximal tubule to increase sodium resorption and stimulation of the adrenal gland to increase aldosterone secretion. Through its actions in the distal nephron—specifically, the late distal convoluted tubule and the collecting duct—aldosterone increases sodium resorption. Aldosterone also stimulates potassium excretion, increasing urinary losses. Along with decreasing urinary loss of sodium, angiotensin II acts as a vasconstrictor, which helps maintain adequate blood pressure in the presence of volume depletion.

Volume expansion stimulates the synthesis of atrial natriuretic peptide, which is produced by the atria in response to atrial wall distention. Along with increasing the GFR, atrial natriuretic peptide inhibits sodium resorption in the medullary portion of the collecting duct, facilitating an increase in urinary sodium excretion.

**Volume overload** occurs when sodium intake exceeds output. In children with kidney failure, there is an impaired ability to excrete sodium. This impairment tends to be proportional to the decrease in the GFR, although in some kidney diseases, such as renal dysplasia and juvenile nephronophthisis, damaged tubules cause significant sodium loss until the GFR is quite low. In general, as the GFR decreases, restriction of sodium intake becomes increasingly necessary. The GFR is low at birth, limiting a newborn's ability to excrete a sodium load. In other situations, there is a loss of the appropriate regulation of renal sodium excretion. This loss occurs in patients with excessive aldosterone, as is seen in primary hyperaldosteronism or renal artery stenosis, wherein excess renal production leads to high aldosterone levels. In acute glomerulonephritis, even without significantly reduced GFR, the normal intrarenal mechanisms that regulate sodium excretion malfunction, causing excessive renal retention of sodium and volume overload.

Renal retention of sodium occurs during volume depletion, but this appropriate response causes the severe excess in total body sodium that is present in heart failure, liver failure, nephrotic syndrome, and other causes of hypoalbuminemia. In these diseases, the effective intravascular volume is decreased, causing the kidney and the various regulatory systems to respond, leading to renal sodium retention and edema formation.

**Volume depletion** usually occurs when sodium losses exceed intake. The most common etiology in children is gastroenteritis. Excessive losses of sodium may also occur from the skin in children with burns, in sweat from patients with cystic fibrosis, or after vigorous exercise. Inadequate intake of sodium is uncommon except in neglect, in famine, or with an inappropriate choice of liquid diet in a child who cannot take solids. Urinary sodium wasting may occur in a range of renal diseases, from renal dysplasia to tubular disorders, such as Bartter syndrome. The neonate, especially if premature, has a mild impairment in the ability to conserve sodium. Iatrogenic renal sodium wasting takes place during diuretic therapy. Renal sodium loss occurs as a result of derangement in the normal regulatory systems. An absence of aldosterone, seen most commonly in children with congenital adrenal hyperplasia caused by 21-hydroxylase deficiency, causes sodium wasting (see Chapter 576).

Isolated disorders of water balance can affect volume status and sodium balance. Because the cell membrane is permeable to water, changes in TBW influence both the extracellular volume and the intracellular volume. In isolated water loss, as occurs in diabetes insipidus, the impact is greater on the intracellular space because of its higher volume compared with the extracellular space. This is why, in comparison with other types of dehydration, hypernatremic dehydration has less impact on plasma volume; most of the fluid loss comes from the intracellular space. Yet, significant water loss eventually affects intravascular volume and will stimulate renal sodium retention, even if total body sodium content is normal. Similarly, with acute water intoxication or SIADH, there is an excess of TBW, but most is in the intracellular space. However, there is some effect on the intravascular volume, which causes renal excretion of sodium. Children with SIADH or water intoxication have high urine sodium concentrations, despite hyponatremia. This finding reinforces the concept that there are independent control systems for water and sodium, yet the 2 systems interact when pathophysiologic processes dictate, and control of effective intravascular volume always takes precedence over control of osmolality.

**Bibliography is available at Expert Consult.**

**55.3 Sodium**

Larry A. Greenbaum

**SODIUM METABOLISM**

**Body Content and Physiologic Function**

Sodium is the dominant cation of the ECF (see Fig. 55-3), and it is the principal determinant of extracellular osmolality. Sodium is therefore necessary for the maintenance of intravascular volume. Less than 3% of sodium is intracellular. More than 40% of total body sodium is in bone; the remainder is in the interstitial and intravascular spaces. The low intracellular sodium concentration, approximately 10 mEq/L, is maintained by Na+/K+-ATPase, which exchanges intracellular sodium for extracellular potassium.

**Intake**

A child's diet determines the amount of sodium ingested—a predominantly cultural determination in older children. An occasional child has salt craving because of an underlying salt-wasting renal disease or adrenal insufficiency. Children in the United States tend to have very high sodium intakes because their diets include a large amount of “junk” food or fast food. Infants receive sodium from breast milk (~7 mEq/L) and formula (7-13 mEq/L, for 20 calorie/oz formula).

Sodium is readily absorbed throughout the gastrointestinal tract. Mineralocorticoids increase sodium transport into the body, although this effect has limited clinical significance. The presence of glucose enhances sodium absorption owing to the presence of a cotransport system. This is the rationale for including sodium and glucose in oral rehydration solutions (see Chapter 340).

**Excretion**

Sodium excretion occurs in stool and sweat, but the kidney regulates sodium balance and is the principal site of sodium excretion. There is some sodium loss in stool, but it is minimal unless diarrhea is present. Normally, sweat has 5-40 mEq/L of sodium. Sweat sodium concentration is increased in children with cystic fibrosis, aldosterone deficiency, or pseudohypoaldosteronism. The higher sweat losses in these conditions may cause or contribute to sodium depletion.

Sodium is unique among electrolytes because water balance, not sodium balance, usually determines its concentration. When the sodium concentration increases, the resultant higher plasma osmolality causes increased thirst and increased secretion of ADH, which leads to renal conservation of water. Both of these mechanisms increase the water content of the body, and the sodium concentration returns to normal. During hyponatremia, the decrease in plasma osmolality stops ADH secretion, and consequent renal water excretion leads to an increase in the sodium concentration. Even though water balance is usually regulated by osmolality, volume depletion does stimulate thirst, ADH secretion, and renal conservation of water. Volume depletion takes precedence over osmolality; volume depletion stimulates ADH secretion, even if a patient has hyponatremia.

The excretion of sodium by the kidney is not regulated by the plasma osmolality. The patient's effective plasma volume determines the amount of sodium in the urine. This is mediated by a variety of regulatory systems, including the renin–angiotensin–aldosterone system and
Bibliography


intrinsic renal mechanisms. In hyponatremia or hypernatremia, the underlying pathophysiology determines the amount of urinary sodium, not the serum sodium concentration.

**HYPERNATREMIA**

Hypernatremia is a sodium concentration >145 mEq/L, although it is sometimes defined as >150 mEq/L. Mild hypernatremia is fairly common in children, especially among infants with gastroenteritis. Hypernatremia in hospitalized patients may be iatrogenic—caused by inadequate water administration or, less often, by excessive sodium administration. Moderate or severe hypernatremia has significant morbidity, including the result of underlying disease, the effects of hypernatremia on the brain, and the risks of overly rapid correction.

**Etiology and Pathophysiology**

There are 3 basic mechanisms of hypernatremia (Table 55-1). Sodium intoxication is frequently iatrogenic in a hospital setting as a result of correction of metabolic acidosis with sodium bicarbonate. Baking soda, a putative home remedy for upset stomach, is another source of sodium bicarbonate. Baking soda, often in a primiparous mother, can cause severe hypernatremic dehydration. Adipsia, the absence of thirst, is usually secondary to damage to the hypothalamus, such as from trauma, tumor, hydrocephalus, or histiocytosis. Primary adipsia is rare.

When hypernatremia occurs in conditions with deficits of sodium and water, the water deficit exceeds the sodium deficit. This occurs only if the patient is unable to ingest adequate water. Diarrhea results in depletion of both sodium and water. Because diarrhea is hypotonic—typical sodium concentration of 35-65 mEq/L—water losses exceed sodium losses, potentially leading to hypernatremia. Most children with gastroenteritis do not have hypernatremia because they drink enough hypotonic fluid to compensate for stool water losses (see Chapter 340). Fluids such as water, juice, and formula are more hypotonic than the stool losses, allowing correction of the water deficit and potentially even causing hyponatremia. Hypernatremia is most likely to occur in the child with diarrhea who has inadequate intake because of emesis, lack of access to water, or anorexia.

Osmotic agents, including mannitol and glucose in diabetes mellitus, cause excessive renal losses of water and sodium. Because the urine is hypotonic (sodium concentration of approximately 50 mEq/L) during an osmotic diuresis, water loss exceeds sodium loss and hypernatremia may occur if water intake is inadequate. Certain chronic kidney diseases, such as renal dysplasia and obstructive uropathy, are associated with tubular dysfunction, leading to excessive losses of sodium and water. Many children with such diseases have disproportionate water loss and are at risk for hypernatremic dehydration, especially if gastroenteritis supervenes. Similar mechanisms occur during the polyuric phase of acute tubular necrosis and after relief of urinary obstruction (postobstructive diuresis). Patients with either condition may have an osmotic diuresis from urinary losses of urea and an inability to conserve water because of tubular dysfunction.

**Clinical Manifestations**

Most children with hypernatremia are dehydrated and show the typical clinical signs and symptoms (see Chapter 57). Children with hypernatremic dehydration tend to have better preservation of intravascular volume because of the shift of water from the intracellular space to the extracellular space. This shift maintains blood pressure and urine output and allows hypernatremic infants to be less symptomatic initially and potentially to become more dehydrated before medical attention is sought. Breastfed infants with hypernatremia are often profoundly dehydrated, with failure to thrive. Probably because of intracellular water loss, the pinned abdominal skin of a dehydrated, hypernatremic infant has a "doughy" feel.

Hypernatremia, even without dehydration, causes central nervous system (CNS) symptoms that tend to parallel the degree of sodium elevation and the acuity of the increase. Patients are irritable, restless, weak, and lethargic. Some infants have a high-pitched cry and hyperventilation or apnea. Alert patients are very thirsty, even though nausea may be present. Hypernatremia may cause fever, although many patients have

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**Table 55-1 Causes of Hypernatremia**

<table>
<thead>
<tr>
<th>EXCESSIVE SODIUM</th>
<th>WATER DEFICIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improperly mixed formula</td>
<td><strong>Nephrogenic diabetes insipidus</strong></td>
</tr>
<tr>
<td>Excess sodium bicarbonate</td>
<td>Acquired</td>
</tr>
<tr>
<td>Ingestion of seawater or sodium chloride</td>
<td>Autosomal recessive (OMIM 222000)</td>
</tr>
<tr>
<td>Intentional salt poisoning (child abuse or Munchausen syndrome by proxy)</td>
<td>Autosomal dominant (OMIM 125800)</td>
</tr>
<tr>
<td>Intravenous hypertonic saline</td>
<td>Central diabetes insipidus</td>
</tr>
<tr>
<td>Hyperaldosteronism</td>
<td>Acquired</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>WATER DEFICIT</th>
<th>GASTROINTESTINAL LOSSES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nephrogenic diabetes insipidus</strong></td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Acquired</td>
<td>Emesis/nasogastric suction</td>
</tr>
<tr>
<td>Autosomal recessive (OMIM 222000)</td>
<td>Osmotic cathartics (lactulose)</td>
</tr>
<tr>
<td>Autosomal dominant (OMIM 125800)</td>
<td>Cutaneous losses</td>
</tr>
<tr>
<td><strong>Central diabetes insipidus</strong></td>
<td>Burns</td>
</tr>
<tr>
<td>Acquired</td>
<td>Excessive sweating</td>
</tr>
<tr>
<td>Autosomal recessive (OMIM 125700)</td>
<td>Renal losses</td>
</tr>
<tr>
<td>Autosomal dominant (OMIM 125700)</td>
<td>Osmotic diuretics (mannitol)</td>
</tr>
<tr>
<td>Wolfram syndrome (OMIM 222300/598500)</td>
<td>Diabetes mellitus</td>
</tr>
</tbody>
</table>

**Increased insensible losses**

- Premature infants
- Radiant warmers
- Phototherapy
- Inadequate intake:
  - Ineffective breastfeeding
  - Child neglect or abuse (adipsia)
  - Adipsia (lack of thirst)

**WATER AND SODIUM DEFICITS**

- **Gastrointestinal losses**
- **Diarrhea**
- **Emesis/nasogastric suction**
- **Osmotic cathartics (lactulose)**
- **Cutaneous losses**
- **Burns**
- **Excessive sweating**
- **Renal losses**
- **Osmotic diuretics (mannitol)**
- **Diabetes mellitus**
- **Chronic kidney disease (dysplasia and obstructive uropathy)**
- **Polyuric phase of acute tubular necrosis**
- **Postobstructive diuresis**

an underlying process that contributes to the fever. Hypernatremia is associated with hyperglycemia and mild hypocalcemia; the mechanisms are unknown. Beyond the sequelae of dehydration, there is no clear direct effect of hypernatremia on other organs or tissues, except the brain.

**Brain hemorrhage** is the most devastating consequence of untreated hypernatremia. As the extracellular osmolality increases, water moves out of brain cells, leading to a decrease in brain volume. This decrease can result in tearing of intracerebral veins and bridging blood vessels as the brain moves away from the skull and the meninges. Patients may have subarachnoid, subdural, and parenchymal hemorrhages. Seizures and coma are possible sequelae of the hemorrhage, although seizures are more common during correction of hypernatremia. The cerebrospinal fluid protein is often elevated in infants with significant hypernatremia, probably owing to leakage from damaged blood vessels. Neonates, especially if premature, seem especially vulnerable to hypernatremia and excessive sodium intake. There is an association between rapid or hyperosmolar sodium bicarbonate administration and the development of intraventricular hemorrhages in neonates. Even though central pontine myelinolysis (CPM) is classically associated with overly rapid correction of hyponatremia, both CPM and extrapontine myelinolysis can occur in children with hypernatremia. Thrombotic complications occur in severe hypernatremic dehydration; they include stroke, dural sinus thrombosis, peripheral thrombosis, and renal vein thrombosis. This is secondary to dehydration and possibly hypercoagulability associated with hypernatremia.

**Diagnosis**

The etiology of hypernatremia is usually apparent from the history. Hypernatremia resulting from water loss occurs only if the patient does not have access to water or is unable to drink. In the absence of dehydration, it is important to ask about sodium intake. Children with excess sodium intake do not have signs of dehydration, unless another process is present. Severe sodium intoxication causes signs of volume overload, such as pulmonary edema and weight gain. Salt poisoning is associated with an elevated fractional excretion of sodium, whereas hypernatremic dehydration causes a low fractional excretion of sodium. In hyperaldosteronism, hypernatremia is usually mild or absent and is associated with edema, hypertension, hypokalemia, and metabolic alkalosis.

When there is isolated water loss, the signs of volume depletion are usually less severe initially because much of the loss is from the intracellular space. When pure water loss causes signs of dehydration, the hypernatremia and water deficit are usually severe. In the child with renal water loss, either central or nephrogenic diabetes insipidus, the urine is inappropriately dilute and urine volume is not low. The urine is maximally concentrated and urine volume is low if the losses are extrarenal or due to inadequate intake. With extrarenal causes of loss of water, the urine osmolality should be $>1,000$ mOsm/kg. When diabetes insipidus is suspected, the evaluation may include measurement of ADH and a water deprivation test, including a trial of desmopresin acetate (synthetic ADH analog) to differentiate between nephrogenic diabetes insipidus and central diabetes insipidus (see Chapters 530 and 558). A water-deprivation test is unnecessary if the patient has simultaneous documentation of hypernatremia and poorly concentrated urine (osmolality lower than that of plasma). In children with central diabetes insipidus, administration of desmopresin acetate increases the urine osmolality above the plasma osmolality, although maximum osmolality does not occur immediately because of the decreased osmolality of the renal medulla as a result of the chronic lack of ADH. In children with nephrogenic diabetes insipidus, there is no response to desmopresin acetate.

With combined sodium and water deficits, analysis of the urine differentiates between renal and nonrenal etiologies. When the losses are extrarenal, the kidney responds to volume depletion with low urine volume, concentrated urine, and sodium retention (urine sodium $<20$ mEq/L, fractional excretion of sodium $<1$%). With renal causes, the urine volume is not appropriately low, the urine is not maximally concentrated, and the urine sodium may be inappropriately elevated.

**Treatment**

As hypernatremia develops, the brain generates idiogenic osmoles to increase the intracellular osmolality and prevent the loss of brain water. This mechanism is not instantaneous and is most prominent when hypernatremia has developed gradually. If the serum sodium concentration is lowered rapidly, there is movement of water from the serum into the brain cells to equalize the osmolality in the 2 compartments (Fig. 55-4). The resultant brain swelling manifests as seizures or coma.

Because of the associated dangers, hypernatremia should not be corrected rapidly. The goal is to decrease the serum sodium by $<12$ mEq/L every 24 hr, a rate of 0.5 mEq/L/hr. The most important component of correcting moderate or severe hypernatremia is frequent monitoring of the serum sodium value so that fluid therapy can be adjusted to provide adequate correction, neither too slow nor too fast. If a child has seizures as a result of brain edema secondary to rapid correction, administration of hypotonic fluid should be stopped. An infusion of 3% saline can acutely increase the serum sodium, reversing the cerebral edema.

In the child with hypernatremic dehydration, as in any child with dehydration, the first priority is restoration of intravascular volume with isotonic fluid (see Chapter 57). Normal saline is preferable to lactated Ringer solution because the lower sodium concentration of the latter can cause the serum sodium to decrease too rapidly, especially if multiple fluid boluses are given. Repeated boluses of normal saline (10-20 mL/kg) may be required to treat hypotension, tachycardia, and signs of poor perfusion (peripheral pulses, capillary refill time) (see Chapters 57 and 70).

The sodium concentration of the deficit replacement fluid, the rate of fluid administration, and the presence of continued water losses determine the rate of decrease of the sodium concentration. The following formula is often cited for calculating the water deficit:

$$\text{Water deficit} = \frac{\text{Body weight} \times 0.6(1-145/\text{current sodium})}{20 \text{ mL/kg}}$$

This calculation is equivalent to 3-4 mL of water per kg for each 1 mEq that the current sodium level exceeds 145 mEq. The utility of such formulas has never been proven in clinical practice. Most patients with hypernatremic dehydration do well with a fluid sodium concentration of approximately half-normal saline, but with a fluid rate that is only 20-30% greater than maintenance fluid. Use of this...
concentration prevents excessive delivery of free water and too rapid a decrease in the serum sodium level. Patients with pure water loss may require a more hypotonic fluid (0.2 normal saline). Excessive water and sodium losses may also need to be replaced. If signs or symptoms of volume depletion develop, the patient receives additional boluses of isotonic saline. Monitoring of the rate of decrease of the serum sodium concentration permits adjustment in the rate and sodium concentration of the fluid that the patient is receiving, avoiding overly rapid correction of the hyponatremia (see Chapter 57 for additional details). Many patients with mild to moderate hypernatremic dehydration as a result of gastroenteritis can be managed with oral rehydration (see Chapter 340).

Acute, severe hypernatremia, usually secondary to sodium administration, can be corrected more rapidly because idiogenic osmoles have not had time to accumulate. This fact balances the high morbidity and mortality rates associated with hypernatremia with the dangers of overly rapid correction. When hypernatremia is severe and is caused by sodium intoxication, it may be impossible to administer enough water to correct the hypernatremia rapidly without worsening the volume overload. In this situation, dialysis allows for removal of the excess sodium, with the precise strategy dependent on the mode of dialysis. In less-severe cases, the addition of a loop diuretic increases the removal of excess sodium and water, decreasing the risk of volume overload. With sodium overload, hypernatremia is corrected with sodium-free intravenous fluid (5% dextrose in water).

Hyperglycemia from hypernatremia is not usually a problem and is not treated with insulin because the acute decrease in glucose may precipitate cerebral edema by lowering plasma osmolality. Rarely, the glucose concentration of intravenous fluids must be reduced (from 5% dextrose in water to 2.5% dextrose in water). The secondary hypocalcemia is treated as needed.

It is important to address the underlying cause of the hypernatremia, if possible. The child with central diabetes insipidus should receive desmopressin acetate. Because this treatment reduces renal excretion of water, excessive intake of water must consequently be avoided to prevent both overly rapid correction of the hypernatremia and the development of hyponatremia. Over the long-term, reduced sodium intake and the use of medications can somewhat ameliorate the water losses in nephrogenic diabetes insipidus (see Chapter 530). The daily water intake of a child who is receiving tube feeding may need to be increased to compensate for high losses. The patient with significant ongoing losses, such as through diarrhea, may need supplemental water and electrolytes (see Chapter 56). Sodium intake is reduced if it contributed to the hypernatremia.

**HYPONATREMIA**

Hyponatremia, a very common electrolyte abnormality in hospitalized patients, is a serum sodium level <135 mEq/L. Both total body sodium and TBW determine the serum sodium concentration. Hyponatremia exists when the ratio of water to sodium is increased. This condition can occur with low, normal, or high levels of body sodium. Similarly, body water can be low, normal, or high.

**Etiology and Pathophysiology**

Table 55-2 lists the causes of hyponatremia. Pseudohyponatremia is a laboratory artifact that is present when the plasma contains very high concentrations of protein (multiple myeloma, intravenous immunoglobulin infusion) or lipid (hypertriglyceridemia, hypercholesterolemia). It does not occur when a direct ion-selective electrode determines the sodium concentration in undiluted plasma, a technique that is used by arterial blood gas analyzers or point-of-care instruments. In true hyponatremia, the measured osmolality is low, whereas it is normal in pseudohyponatremia. Hyperosmolality, as may occur with hyperglycemia, causes a low serum sodium concentration because water moves down its osmotic gradient from the intracellular space into the extracellular space, diluting the sodium concentration. However, because the manifestations of hyponatremia are a result of the low plasma osmolality, patients with hyponatremia resulting from hyperosmolality do not have symptoms of hyponatremia. When the etiology of the hyperosmolality resolves, such as hyperglycemia in diabetes mellitus, water moves back into the cells and the sodium concentration rises to its "true" value. Mannitol or sucrose, a component of intravenous immunoglobulin preparations, may cause hyponatremia because of hyperosmolality.

Classification of hyponatremia is based on the patient’s volume status. In hypovolemic hyponatremia, the child has lost sodium from the body. The water balance may be positive or negative, but sodium loss has been higher than water loss. The pathogenesis of the

<table>
<thead>
<tr>
<th>Table 55-2 Causes of Hyponatremia</th>
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<tbody>
<tr>
<td><strong>PSEUDOHYponATREMIA</strong></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
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<tr>
<td>Hyperproteinemia</td>
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<tr>
<td><strong>HYPEROSMOLALITY</strong></td>
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<tr>
<td>Hyperglycemia</td>
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<tr>
<td>Intravenous (mannitol, sucrose, glycerine)</td>
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<tr>
<td><strong>HYPOVOLEMIC HY PonATREMIA</strong></td>
</tr>
<tr>
<td><strong>EXTRARENAL LOSSES</strong></td>
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<tr>
<td>Gastrointestinal (emesis, diarrhea)</td>
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<tr>
<td>Skin (sweating or burns)</td>
</tr>
<tr>
<td>Third space losses (bowel obstruction, peritonitis, sepsis)</td>
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<tr>
<td><strong>RENAL LOSSES</strong></td>
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<tr>
<td>Thiazide or loop diuretics</td>
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<tr>
<td>Osmotic diuresis</td>
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<td>Postobstructive diuresis</td>
</tr>
<tr>
<td>Polyuric phase of acute tubular necrosis</td>
</tr>
<tr>
<td>Juvenile nephronophthisis (OMIM 256100/606966/602088/604387/611498)</td>
</tr>
<tr>
<td>Autosomal recessive polycystic kidney disease (OMIM 263200)</td>
</tr>
<tr>
<td>Tubulointerstitial nephritis</td>
</tr>
<tr>
<td>Obstructive uropathy</td>
</tr>
<tr>
<td>Cerebral salt wasting</td>
</tr>
<tr>
<td>Proximal (type II) renal tubular acidosis (OMIM 604278)*</td>
</tr>
<tr>
<td>Lack of aldosterone effect (high serum potassium):</td>
</tr>
<tr>
<td>Absence of aldosterone (e.g., 21-hydroxylase deficiency [OMIM 201910])</td>
</tr>
<tr>
<td>Pseudohypoaldosteronism type I (OMIM 264350/177735)</td>
</tr>
<tr>
<td>Urinary tract obstruction and/or infection</td>
</tr>
<tr>
<td><strong>EUVOLEMIC HY PonATREMIA</strong></td>
</tr>
<tr>
<td>Syndrome of inappropriate antidiuretic hormone secretion</td>
</tr>
<tr>
<td>Nephrogenic syndrome of inappropriate antidiuresis (OMIM 304800)</td>
</tr>
<tr>
<td>Desmopressin acetate</td>
</tr>
<tr>
<td>Glucocorticoid deficiency</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Water intoxication:</td>
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<tr>
<td>Intravenous (excess hypotonic intravenous fluids)</td>
</tr>
<tr>
<td>Feeding infants excessive water products</td>
</tr>
<tr>
<td>Swimming lessons</td>
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<tr>
<td>Tap water enema</td>
</tr>
<tr>
<td>Child abuse</td>
</tr>
<tr>
<td>Psychogenic polydipsia</td>
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<tr>
<td>Diluted formula</td>
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<tr>
<td>Beer potomania</td>
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<tr>
<td>Exercise-induced hyponatremia</td>
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<tr>
<td><strong>HYPOVOREMIC HY PonATREMIA</strong></td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Acute, chronic kidney injury</td>
</tr>
<tr>
<td>Capillary leak caused by sepsis</td>
</tr>
<tr>
<td>Hypoalbuminemia caused by gastrointestinal disease (protein-losing enteropathy)</td>
</tr>
</tbody>
</table>

*Most cases of proximal renal tubular acidosis are not caused by this primary genetic disorder. Proximal renal tubular acidosis is usually part of Fanconi syndrome, which has multiple etiologies.

hypoventilation is usually a combination of sodium loss and water retention to compensate for the volume depletion. The patient has a pathologic increase in fluid loss, and this fluid contains sodium. Most fluid that is lost has a lower sodium concentration than that of plasma. Viral diarrhea fluid has, on average, a sodium concentration of 50 mEq/L. Replacing diarrhea fluid, which has a sodium concentration of 50 mEq/L, with formula, which has only approximately 10 mEq/L of sodium, reduces the sodium concentration. Intravascular volume depletion interferes with renal water excretion, the body’s usual mechanism for preventing hyponatremia. The volume depletion stimulates ADH synthesis, resulting in renal water retention. Volume depletion also decreases the GFR and enhances water resorption in the proximal tubule, thereby reducing water delivery to the collecting duct.

Diabetes is a result of gastroenteritis in young children. Emesis causes hyponatremia if the patient takes in hypotonic fluid, either intravenously or enterally, despite the emesis. Most patients with emesis have either a normal sodium concentration or hyponatremia. Burns may cause massive losses of isotonic fluid and resultant volume depletion. Hyponatremia develops if the patient receives hypotonic fluid. Losses of sodium from sweat are especially high in children with cystic fibrosis, aldosterone deficiency, or pseudohypoaldosteronism, although high losses can occur simply in a hot climate. Third-space losses are isotonic and can cause significant volume depletion, leading to ADH production and water retention, which can cause hyponatremia if the patient receives hypotonic fluid. In diseases that cause volume depletion through extrarenal sodium loss, the urine sodium level should be low (<10 mEq/L) as part of the renal response to maintain the intravascular volume. The only exceptions are diseases that cause both extrarenal and renal sodium losses: adrenal insufficiency and pseudohypoaldosteronism.

Renal sodium loss may occur in a variety of situations. In some situations, the urine sodium concentration is >140 mEq/L; thus, hyponatremia may occur without any fluid intake. In many cases, the urine sodium level is less than the serum concentration; thus, the intake of hypotonic fluid is necessary for hyponatremia to develop. In diseased associated with urinary sodium loss, the urine sodium level is >20 mEq/L despite volume depletion. This may not be true if the urinary sodium loss is no longer occurring, as is frequently the case if diuretics are discontinued. Because loop diuretics prevent generation of a maximally hypertonic renal medulla, the patient can neither maximally dilute nor concentrate the urine. The inability to maximally retain water provides some protection against severe hyponatremia. The patient receiving thiazide diuretics can concentrate the urine and is at higher risk for severe hyponatremia. Osmotic agents, such as glucose during diabetic ketoacidosis, cause loss of both water and sodium. Urea accumulates during renal failure and then acts as an osmotic diuretic after relief of urinary tract obstruction and during the polyuric phase of acute tubular necrosis. Transient tubular damage in these conditions further impairs sodium conservation. The serum sodium concentration in these conditions depends on the sodium concentration of the fluid used to replace the losses. Hyponatremia develops when the fluid is hypotonic relative to the urinary losses.

Renal salt wasting occurs in hereditary kidney diseases, such as juvenile nephronophthisis and autosomal recessive polycystic kidney disease. Obstructive uropathy, most commonly a consequence of posterior urethral valves, produces salt wasting, but patients with the disease may also have hyponatremia as a result of impaired ability to concentrate urine and high water loss. Acquired tubulointerstitial nephritis, usually secondary to either medications or infections, may cause salt wasting, along with other evidence of tubular dysfunction. CNS injury may produce cerebral salt wasting, which is theoretically caused by the production of a natriuretic peptide that causes renal salt wasting. In type II renal tubular acidosis (RTA), usually associated with Fanconi syndrome (see Chapter 529.1), there is increased excretion of sodium and bicarbonate in the urine. Patients with Fanconi syndrome also have glycosuria, aminoaciduria, and hypophosphatemia because of renal phosphate wasting.

Aldosterone is necessary for renal sodium retention and for the excretion of potassium and acid. In congenital adrenal hyperplasia caused by 21-hydroxylase deficiency, the block of aldosterone production results in hyponatremia, hyperkalemia, and metabolic acidosis. In pseudohypoaldosteronism, aldosterone levels are elevated, but there is no response because of either a defective sodium channel or a deficiency of aldosterone receptors. A lack of tubular response to aldosterone may occur in children with urinary tract obstruction, especially during an acute urinary tract infection.

In hypervolemic hyponatremia, there is an excess of TBW and sodium, although the increase in water is greater than the increase in sodium. In most of the conditions that cause hypervolemic hyponatremia, there is a decrease in the effective blood volume, resulting from third space fluid loss, vasodilation, or poor cardiac output. The regulatory systems sense a decrease in effective blood volume and attempt to retain water and sodium to correct the problem. ADH causes renal water retention, and the kidney, under the influence of aldosterone and other intrarenal mechanisms, retains sodium. The patient’s sodium concentration decreases because water intake exceeds sodium intake and ADH prevents the normal loss of excess water.

In these disorders, there is a low urine sodium concentration (<10 mEq/L) and an excess of both TBW and sodium. The only exception is in patients with renal failure and hyponatremia. These patients have an expanded intravascular volume, and hyponatremia can therefore appropriately suppress ADH production. Water cannot be excreted because very little urine is being made. Serum sodium is diluted through ingestion of water. Because of renal dysfunction, the urine sodium concentration may be elevated, but urine volume is so low that urine sodium excretion has not kept up with sodium intake, leading to sodium overload. The urine sodium concentration in renal failure varies. In patients with acute glomerulonephritis, because it does not affect the tubules, the urine sodium level is usually low, whereas in patients with acute tubular necrosis, it is elevated because of tubular dysfunction.

Patients with hyponatremia and no evidence of volume overload or volume depletion have euclidean hyponatremia. These patients typically have an excess of TBW and a slight decrease in total body sodium. Some of these patients have an increase in weight, implying that they are volume-overloaded. Nevertheless, from a clinical standpoint, they usually appear normal or have subtle signs of fluid overload.

In SIADH, the secretion of ADH is not inhibited by either low serum osmolality or expanded intravascular volume (see Chapter 559). The result is that the child with SIADH is unable to excrete water. This results in dilution of the serum sodium and hyponatremia. The expansion of the extracellular volume as a result of the retained water causes a mild increase in intravascular volume. The kidney increases sodium excretion in an effort to decrease intravascular volume to normal; thus, the patient has a mild decrease in body sodium. SIADH most commonly occurs with disorders of the CNS (infection, hemorrhage, trauma, tumor, thrombosis), but lung disease (infection, asthma, positive pressure ventilation) and malignant tumors (producing ADH) are other potential causes. A variety of medications may cause SIADH, including recreational use of 3,4-methylenedioxymethylamphetamines (MDMA, or “Ecstasy”), opiates, antiepileptic drugs (carbamazepine, oxcarbazepine, valproate), tricyclic antidepressants, vincristine, Cytoxan, and selective serotonin reuptake inhibitors. The diagnosis of SIADH is one of exclusion, because other causes of hyponatremia must be eliminated (Table 55-3). Because SIADH is a state of intravascular volume expansion, low serum uric acid and BUN levels are supportive of the diagnosis.

A rare gain-of-function mutation in the renal ADH receptor causes nephrogenic syndrome of inappropriate antidiuresis. Patients with this X-linked disorder appear to have SIADH but have undetectable levels of ADH.

Hyponatremia in hospitalized patients is frequently caused by inappropriate production of ADH and administration of hypotonic intravenous fluids. Causes of inappropriate ADH production include stress, medications such as narcotics or anesthetics, nausea, and respiratory illness. The synthetic analog of ADH, desmopressin acetate, causes...
water retention and may cause hyponatremia if fluid intake is not appropriately limited. The main uses of desmopressin acetate in children are for the management of central diabetes insipidus and of nocturnal enuresis.

**Excess water ingestion** can produce hyponatremia. In these cases, the sodium concentration decreases as a result of dilution. This decrease suppresses ADH secretion, and there is a marked water diuresis by the kidney. Hyponatremia develops only because the intake of water exceeds the kidney's ability to eliminate water. This condition is more likely to occur in infants because their lower GFR limits their ability to excrete water.

Hyponatremia may develop in infants <6 mo of age when caregivers offer water to their infants as a supplement, during hot weather, or when they run out of formula. Hyponatremia may result in transient seizures, hypothermia, and poor tone. With cessation of water intake, the hyponatremia rapidly corrects. Infants <6 mo of age should not be given water to drink; infants between 6 and 12 mo of age should not receive more than 1-2 ounces. If the infant appears thirsty, the parent should offer formula or breastfeed the child.

In some situations, the water intoxication causes acute hyponatremia and is a consequence of a massive acute water load. Examples of causes of this water load include infant swimming lessons, inappropriate use of hypotonic intravenous fluids, water enemas, and forced water intake as a form of child abuse. Chronic hyponatremia occurs in children who receive water, but limited sodium and protein. The minimum urine osmolality is approximately 50 mOsm/kg, the kidney can excrete 1 L of water only if there is enough solute ingested to produce 50 mOsm for urinary excretion. Because sodium and urea (a breakdown product of protein) are the principal urinary solutes, a lack of intake of sodium and protein prevents adequate water excretion. This occurs with the use of diluted formula or other inappropriate diets. Subsistence on beer, a poor source of sodium and protein, causes hyponatremia because of the inability to excrete the high water load ("beer potomania"). **Exercise-induced hyponatremia**, reported commonly during marathons, is caused by excessive water intake, salt losses from sweat, and secretion of ADH.

The pathogenesis of the hyponatremia in glucocorticoid deficiency is multifactorial, and includes increased ADH secretion. In hypoaldosteronism, there is an inappropriate retention of water by the kidney, but the precise mechanisms are not clearly elucidated.

**Clinical Manifestations**

Hyponatremia causes a decrease in the osmolality of the extracellular space. Because the intracellular space then has a higher osmolality, water moves from the extracellular space to the intracellular space to maintain osmotic equilibrium. The increase in intracellular water causes cells to swell. Although cell swelling is not problematic in most tissues, it is dangerous for the brain, which is confined by the skull. As brain cells swell, there is an increase in intracranial pressure, which impairs cerebral blood flow. Acute, severe hyponatremia can cause brainstem herniation and apnea; respiratory support is often necessary. Brain cell swelling is responsible for most of the symptoms of hyponatremia. Neurologic symptoms of hyponatremia include anorexia, nausea, emesis, malaise, lethargy, confusion, agitation, headache, seizures, coma, and decreased reflexes. Patients may have thermoregulatory and Cheyne-Stokes respirations. Hyponatremia can cause muscle cramps and weakness; rhabdomyolysis can occur with water intoxication.

The symptoms of hyponatremia are mostly a result of the decrease in extracellular osmolality and the resulting movement of water down its osmotic gradient into the intracellular space. Brain swelling can be significantly obviated if the hyponatremia develops gradually, because brain cells adapt to the decreased extracellular osmolality by reducing intracellular osmolality. This reduction is achieved by excretion of the main intracellular ions (potassium and chloride) and a variety of small organic molecules. This process explains why the range of symptoms in hyponatremia is related to both the serum sodium level and its rate of decrease. A patient with chronic hyponatremia may have only subtle neurologic abnormalities with a serum sodium level of 110 mEq/L, but another patient may have seizures because of an acute decline in serum sodium level from 140 to 125 mEq/L.

**Diagnosis**

The history usually points to a likely etiology of the hyponatremia. Most patients with hyponatremia have a history of volume depletion. Diarrhea and diuretic use are very common causes of hyponatremia in children. A history of polyuria, perhaps with enuresis, and/or salt craving is present in children with primary kidney diseases or absence of aldosterone effect. Children may have signs or symptoms suggesting a diagnosis of hypothyroidism or adrenal insufficiency (see Chapters 565 and 575). Brain injury raises the possibility of SIADH or cerebral salt wasting, with the caveat that SIADH is much more likely. Liver disease, nephrotic syndrome, renal failure, or congestive heart failure may be acute or chronic. The history should include a review of the patient’s intake, both intravenous and enteral, with careful attention to the amounts of water, sodium, and protein.

The traditional first step in the diagnostic process is determination of the plasma osmolality. This is done because some patients with a low serum sodium value do not have low osmolality. The clinical effects of hyponatremia are secondary to the associated low osmolality. Without a low osmolality, there is no movement of water into the intracellular space. A patient with hyponatremia can have a low, normal, or high osmolality. A normal osmolality in combination with hyponatremia occurs in pseudohyponatremia. Children with elevation of serum glucose concentration or of another effective solute (mannitol) have a high plasma osmolality and hyponatremia. The presence of a low osmolality indicates "true" hyponatremia. Patients with low osmolality are at risk for neurologic symptoms and require further evaluation to determine the etiology of the hyponatremia.

In some situations, true hyponatremia is present despite a normal or elevated plasma osmolality. The presence of an ineffective osmole, most commonly urea, increases the plasma osmolality, but because the osmole has the same concentration in the intracellular space, it does not cause fluid to move into the extracellular space. There is no dilution of the serum sodium by water, and the sodium concentration remains unchanged if the ineffective osmole is eliminated. Most importantly, the ineffective osmole does not protect the brain from edema caused by hyponatremia. Hence, a patient may have symptoms of hyponatremia despite having a normal or increased osmolality because of uremia.

In patients with true hyponatremia, the next step in the diagnostic process is to clinically evaluate the volume status. Patients with hyponatremia can be hypovolemic, hypervolemic, or euvoolemic. The diagnosis of volume depletion relies on the usual findings with dehydration (see Chapter 57), although subtle volume depletion may not be clinically apparent. In a patient with subtle volume depletion, a fluid bolus results in a decrease in the urine osmolality and an increase in the serum sodium concentration. Children with hypervolemia are edematous on physical examination. They may have ascites, pulmonary edema, pleural effusion, or hypertension.

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**Table 55-3**

<table>
<thead>
<tr>
<th>Diagnostic Criteria for Syndrome of Inappropriate Antidiuretic Hormone Secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of:</td>
</tr>
<tr>
<td>Renal, adrenal, or thyroid insufficiency</td>
</tr>
<tr>
<td>Heart failure, nephrotic syndrome, or cirrhosis</td>
</tr>
<tr>
<td>Diuretic ingestion</td>
</tr>
<tr>
<td>Dehydration</td>
</tr>
<tr>
<td>Urine osmolality &gt;100 mOsm/kg (usually &gt; plasma)</td>
</tr>
<tr>
<td>Serum osmolality &lt;280 mOsm/kg and serum sodium &lt;135 mEq/L</td>
</tr>
<tr>
<td>Urine sodium &gt;30 mEq/L</td>
</tr>
<tr>
<td>Reversal of “sodium wasting” and correction of hyponatremia with water restriction</td>
</tr>
</tbody>
</table>
Hypovolemic hyponatremia can have renal or nonrenal causes. The urine sodium concentration is very useful in differentiating between renal and nonrenal causes. When the losses are nonrenal and the kidney is working properly, there is renal retention of sodium, a normal homeostatic response to volume depletion. Thus, the urinary sodium concentration is low, typically <10 mEq/L, although sodium conservation in neonates is less avid. When the kidney is the cause of the sodium loss, the urine sodium concentration is >20 mEq/L, reflecting the defect in renal sodium reabsorption. The interpretation of the urine sodium level is challenging with diuretic therapy because it is high when diuretics are being used but low after the diuretic effect is gone. This becomes an issue only when diuretic use is surreptitious. The urine sodium concentration is not useful if a metabolic alkalosis is present; the urine chloride concentration must be used instead (see Chapter 55.7).

Differentiating among the nonrenal causes of hypovolemic hyponatremia is usually facilitated by the history. Although the renal causes are more challenging to distinguish, a high serum potassium concentration is associated with disorders in which the sodium wasting is caused by absence of or ineffectiveness of aldosterone.

In the patient with hypervolemic hyponatremia, the urine sodium concentration is a helpful parameter. It is usually <10 mEq/L, except in the patient with renal failure.

**Treatment**

The management of hyponatremia is based on the pathophysiology of the specific etiology. The management of all causes requires judicious monitoring and avoidance of an overly quick normalization of the serum sodium concentration. A patient with severe symptoms (seizures), no matter the etiology, should be given a bolus of hypertonic saline to produce a small, rapid increase in serum sodium. Hypoxia worsens cerebral edema, and hyponatremia may cause hypoxia. Hence, pulse oximetry should be monitored, and hypoxia aggressively corrected.

With all causes of hyponatremia, it is important to avoid "overly rapid" correction. The reason is that rapid correction of hyponatremia may cause CPM. This syndrome, which occurs within several days of rapid correction of hyponatremia, produces neurologic symptoms, including confusion, agitation, flaccid or spastic quadriaparesis, and death. There are usually characteristic pathologic and radiologic changes in the brain, especially in the pons, but extrapontine lesions are quite common and may cause additional symptoms. Despite severe symptoms, full recovery does occur in some patients.

CPM is more common in patients who are treated for chronic hyponatremia than in those treated for acute hyponatremia. Presumably, this difference is based on the adaptation of brain cells to the hyponatremia. The reduced intracellular osmolality that is an adaptive mechanism for chronic hyponatremia makes brain cells susceptible to dehydration during rapid correction of the hyponatremia, and this may be the mechanism of CPM. Even though CPM is rare in pediatric patients, it is advisable to avoid correcting the serum sodium concentration by >12 mEq/L/24 hr or >18 mEq/L/48 hr. Desmopressin is a potential option if the serum sodium level is increasing too rapidly. This guideline does not apply to acute hyponatremia, as may occur with water intoxication, because the hyponatremia is more often symptomatic and there has not been time for the adaptive decrease in brain osmolality to occur. The consequences of brain edema in acute hyponatremia exceed the small risk of CPM.

Patients with hyponatremia can have severe neurologic symptoms, such as seizures and coma. The seizures associated with hyponatremia generally are poorly responsive to anticonvulsants. The child with hyponatremia and severe symptoms needs to receive treatment that will quickly reduce cerebral edema. This goal is best accomplished by increasing the extracellular osmolality so that water moves down its osmolar gradient from the intracellular space to the extracellular space.

Intravenous hypertonic saline rapidly increases serum sodium, and the effect on serum osmolality leads to a decrease in brain edema. Each mL/kg of 3% sodium chloride increases the serum sodium by approximately 1 mEq/L. A child with active symptoms often improves after receiving 4-6 mL/kg of 3% sodium chloride. The child with hypovolemic hyponatremia has a deficiency in sodium and may have a deficiency in water. The cornerstone of therapy is to replace the sodium deficit and any water deficit that is present. The first step in treating any dehydrated patient is to restore the intravascular volume with isotonic saline. Ultimately, complete restoration of intravascular volume suppresses ADH production, thereby permitting excretion of the excess water. Chapter 57 discusses the management of hyponatremic dehydration.

The management of hypervolemic hyponatremia is difficult. Patients with this disorder have an excess of both water and sodium. Administration of sodium leads to worsening volume overload and edema. In addition, the patients are retaining water and sodium because of their ineffective intravascular volume or renal insufficiency. The cornerstone of therapy is water and sodium restriction, because the patients have volume overload. Diuretics may help by causing excretion of both sodium and water. Vasopressin antagonists, by blocking the action of ADH and causing a water diuresis, are effective in correcting the hypervolemic hyponatremia caused by heart failure or cirrhosis.

Some patients with low albumin resulting from nephrotic syndrome have a better response to diuretics after an infusion of 25% albumin; the sodium concentration often normalizes as a result of expansion of the intravascular volume. A child with heart failure may have an increase in renal water and sodium excretion if there is an improvement in cardiac output. This improvement will "turn off" the regulatory hormones that are causing renal water (ADH) and sodium (aldosterone) retention. The patient with renal failure cannot respond to any of these therapies except fluid restriction. Insensible fluid losses eventually result in an increase in the sodium concentration as long as insensible and urinary losses are greater than intake. A more definitive approach in children with renal failure is to perform dialysis, which removes water and sodium.

In isovolumic hyponatremia, there is usually an excess of water and a mild sodium deficit. Therapy is directed at eliminating the excess water. The child with acute severe water intake loses water in the urine because ADH production is turned off as a result of the low plasma osmolality. Children may correct their hyponatremia spontaneously over 3-6 hr. For acute, symptomatic hyponatremia as a result of water intoxication, hypertonic saline may be needed to reverse cerebral edema. For chronic hyponatremia from poor solute intake, the child needs to receive an appropriate formula, and excess water intake should be eliminated.

Children with iatrogenic hyponatremia caused by the administration of hypertonic intravenous fluids should receive 3% saline if they are symptomatic. Subsequent management is dictated by the patient's volume status. The hypovolemic child should receive isotonic intravenous fluids. The child with nonphysiologic stimuli for ADH production should undergo fluid restriction. Prevention of this iatrogenic complication requires judicious use of intravenous fluids (see Chapter 56).

Specific hormone replacement is the cornerstone of therapy for the hyponatremia of hypothyroidism or cortisol deficiency. Correction of the underlying defect permits appropriate elimination of the excess water. SIA DH is a condition of excess water, with limited ability of the kidney to excrete water. The mainstay of its therapy is fluid restriction. Furosemide is effective in the patient with SIA DH and severe hyponatremia. Even in a patient with SIA DH, furosemide causes an increase in water and sodium excretion. The loss of sodium is somewhat counterproductive, but this sodium can be replaced with hypertonic saline. Because the patient has a net loss of water and the urinary losses of sodium have been replaced, there is an increase in the sodium concentration, but no significant increase in blood pressure. Vasopressin antagonists (conivaptan, lixivaptan, tolvaptan), which block the action of ADH and cause a water diuresis, are effective at correcting hyponatremic hyponatremia, but overly rapid correction is a potential complication.

Treatment of chronic SIA DH is challenging. Fluid restriction in children is difficult for nutritional and behavioral reasons. Other
options are long-term furosemide therapy with sodium supplementation, an oral vasopressin antagonist (tolvaptan), or oral urea.

**Bibliography is available at Expert Consult.**

### 55.4 Potassium

**Larry A. Greenbaum**

#### POTASSIUM METABOLISM

**Body Content and Physiologic Function**

The intracellular concentration of potassium, approximately 150 mEq/L, is much higher than the plasma concentration (see Fig. 55-3). The majority of body potassium is contained in muscle. As muscle mass increases, there is an increase in body potassium. There is thus an increase in body potassium during puberty, and it is more significant in males. The majority of extracellular potassium is in bone; <1% of total body potassium is in plasma.

Because most potassium is intracellular, the plasma concentration does not always reflect the total body potassium content. A variety of conditions alter the distribution of potassium between the intracellular and extracellular compartments. The Na⁺,K⁺-ATPase maintains the high intracellular potassium concentration by pumping sodium out of the cell and potassium into the cell. This activity balances the normal leak of potassium out of cells via potassium channels that is driven by the favorable chemical gradient. Insulin increases potassium movement into cells by activating the Na⁺,K⁺-ATPase. A decrease in pH drives potassium extracellularly; an increase in pH has the opposite effect. β-Adrenergic agonists stimulate the Na⁺,K⁺-ATPase, increasing cellular uptake of potassium. This increase is protective, in that hyperkalemia stimulates adrenomedullary release of catecholamines. α-Adrenergic agonists and exercise cause a net movement of potassium out of the intracellular space. An increase in plasma osmolality, as with mannitol infusion, leads to water movement out of the cells, and potassium follows as a result of solvent drag. The serum potassium concentration increases by approximately 0.6 mEq/L with each 10-mOsm rise in plasma osmolality.

The high intracellular concentration of potassium, the principal intracellular cation, is maintained via the Na⁺,K⁺-ATPase. The resulting chemical gradient is used to produce the resting membrane potential of cells. Potassium is necessary for the electrical responsiveness of nerve and muscle cells and for the contractility of cardiac, skeletal, and smooth muscle. The changes in membrane polarization that occur during muscle contraction or nerve conduction make these cells susceptible to changes in serum potassium levels. The ratio of intracellular to extracellular potassium determines the threshold for a cell to generate an action potential and the rate of cellular repolarization. The intracellular potassium concentration affects cellular enzymes. Potassium is necessary for maintaining cell volume because of its important contribution to intracellular osmolality.

**Intake**

Potassium is plentiful in food. Dietary consumption varies considerably, even though 1-2 mEq/kg is the recommended intake. The intestines normally absorb approximately 90% of ingested potassium. Most absorption occurs in the small intestine, whereas the colon exchanges body potassium for luminal sodium. Regulation of intestinal losses normally has a minimal role in maintaining potassium homeostasis, although renal failure, aldosterone, and glucocorticoids increase colonic secretion of potassium. The increase in intestinal losses in the setting of renal failure and hyperkalemia, which stimulates aldosterone production, is clinically significant, helping to protect against hyperkalemia.

**Excretion**

There is some loss of potassium in sweat, but it is normally minimal. The colon has the ability to eliminate some potassium. In addition, after an acute potassium load, much of the potassium, >40%, moves intracellularly, through the actions of epinephrine and insulin, which are produced in response to hyperkalemia. This process provides transient protection from hyperkalemia, but most ingested potassium is eventually excreted in the urine. The kidneys principally regulate long-term potassium balance, and they alter excretion in response to a variety of signals. Potassium is freely filtered at the glomerulus, but 90% is resorbed before the distal tubule and collecting duct, the principal sites of potassium regulation. The distal tubule and the collecting duct have the ability to absorb and secrete potassium. It is the amount of tubular secretion that regulates the amount of potassium that appears in the urine. The plasma potassium concentration directly influences secretion in the distal nephron. As the potassium concentration increases, secretion increases.

The principal hormone regulating potassium secretion is aldosterone, which is released by the adrenal cortex in response to increased plasma potassium. Its main site of action is the cortical collecting duct, where aldosterone stimulates sodium movement from the tubule into the cells. This movement creates a negative charge in the tubular lumen, facilitating potassium excretion. In addition, the increased intracellular sodium stimulates the basolateral Na⁺,K⁺-ATPase, causing more potassium to move into the cells lining the cortical collecting duct. Glucocorticoids, ADH, a high urinary flow rate, and high sodium delivery to the distal nephron also increase urinary potassium excretion. Potassium excretion is decreased by insulin, catecholamines, and urinary ammonia. Whereas ADH increases potassium secretion, it also causes water resorption, decreasing urinary flow. The net effect is that ADH has little overall impact on potassium balance. Alkalosis causes potassium to move into cells, including the cells lining the collecting duct. This movement increases potassium secretion, and because acidosis has the opposite effect, it decreases potassium secretion.

The kidney can dramatically vary potassium excretion in response to changes in intake. Normally, approximately 10-15% of the filtered load is excreted. In an adult, excretion of potassium can vary from 5-1,000 mEq/day.

#### HYPERKALEMIA

Hyperkalemia—because of the potential for lethal arrhythmias—is one of the most alarming electrolyte abnormalities.

**Etiology and Pathophysiology**

Three basic mechanisms cause hyperkalemia (Table 55-4). In the individual patient, the etiology is sometimes multifactorial.

**Spurious hyperkalemia or pseudohyperkalemia** is very common in children because of the difficulties in obtaining blood specimens. This laboratory result is usually caused by hemolysis during a heparinized or phlebotomy, but it can be the result of prolonged tourniquet application or fist clenching, either of which causes local potassium release from muscle.

The serum potassium level is normally 0.4 mEq/L higher than the plasma value, secondary to potassium release from cells during clot formation. This phenomenon is exaggerated with thrombocytosis because of potassium release from platelets. For every 100,000/m³ increase in the platelet count, the serum potassium level rises by approximately 0.15 mEq/L. This phenomenon also occurs with the marked white blood cell count elevations sometimes seen with leukemia. Elevated white blood cell counts, typically >200,000/m³, can cause a dramatic elevation in the serum potassium concentration. Analysis of a plasma sample usually provides an accurate result. It is important to analyze the sample promptly to avoid potassium release from cells, which occurs if the sample is stored in the cold, or cellular uptake of potassium and spurious hypokalemia, which occurs with storage of the sample at room temperature. Occasionally, heparin causes lysis of leukemic cells and a false elevation of the plasma sample; a blood gas syringe has less heparin and may provide a more accurate reading than a standard tube. There are rare genetic disorders causing leakage of potassium from red cells that may cause familial pseudohyperkalemia.
Bibliography


Because of the kidney’s ability to excrete potassium, it is unusual for excessive intake, by itself, to cause hyperkalemia. This condition can occur in a patient who is receiving large quantities of intravenous or oral potassium for excessive losses that are no longer present. Frequent or rapid blood transfusions can acutely increase the potassium level because of the potassium content of blood, which is variably elevated. Increased intake may precipitate hyperkalemia if there is an underlying defect in potassium excretion.

The intracellular space has a very high potassium concentration, so a shift of potassium from the intracellular space to the extracellular space can have a significant effect on the plasma potassium level. This shift occurs with metabolic acidoses, but the effect is minimal with an organic acid (lactic acidosis, ketoacidosis). A respiratory acidosis has less impact than a metabolic acidoses. Cell destruction, as seen with rhabdomyolysis, tumor lysis syndrome, tissue necrosis, or hemolysis, releases potassium into the extracellular milieu. The potassium released from red blood cells in internal bleeding, such as hematomas, is resorbed and enters the extracellular space.

Normal doses of succinylcholine or β-blockers and fluoride or digitalis intoxication all cause a shift of potassium out of the intracellular compartment. Succinylcholine should not be used during anesthesia in patients at risk for hyperkalemia. β-Blockers prevent the normal cellular uptake of potassium mediated by binding of β-agonists to the β-adrenergic receptors. Potassium release from muscle cells occurs during exercise, and levels can increase by 1-2 mEq/L with high activity. With an increased plasma osmolality, water moves from the intracellular space and potassium follows. This process occurs with hyperglycemia, although in nondiabetic patients, the resultant increase in insulin causes potassium to move intracellularly. In diabetic ketoacidosis, the absence of insulin causes potassium to leave the intracellular space, and the problem is compounded by the hyperosmolality. The effect of hyperosmolality causes a transcellular shift of potassium into the extracellular space after mannitol or hypertonic saline infusions. Malignant hyperthermia, which is triggered by some inhaled anesthetics, causes muscle release of potassium (see Chapter 611.2). Hyperkalemic periodic paralysis is an autosomal dominant disorder caused by a mutated sodium channel. It results in episodic cellular release of potassium and attacks of paralysis (see Chapter 611.1).

The kidneys excrete most of the daily potassium intake, so a decrease in kidney function can cause hyperkalemia. Newborn infants in general, and especially premature infants, have decreased kidney function at birth and thus are at increased risk for hyperkalemia despite an absence of intrinsic renal disease. Neonates also have decreased expression of potassium channels, further limiting potassium excretion.

A wide range of primary adrenal disorders, both hereditary and acquired, can cause decreased production of aldosterone, with secondary hyperkalemia (see Chapters 575 and 576). Patients with these disorders typically have metabolic acidosis and salt wasting with hypernatremia. Children with more subtle adrenal insufficiency may have electrolyte problems only during acute illnesses. The most common form of congenital adrenal hyperplasia, 21-hydroxylase deficiency, typically manifests in male infants as hyperkalemia, metabolic acidosis, hypernatremia, and volume depletion. Females with this disorder usually are diagnosed as newborns because of their ambiguous genitalia; treatment prevents the development of electrolyte problems.

Renin, via angiotensin II, stimulates aldosterone production. A deficiency in renin, a result of kidney damage, can lead to decreased aldosterone production. Hyporeninemia occurs in many kidney diseases, with some of the more common pediatric causes listed in Table 55-4. These patients typically have hyperkalemia and a metabolic acidosis, without hypernatremia. Some of these patients have impaired renal function, partially accounting for the hyperkalemia, but the impairment in potassium excretion is more extreme than expected for the degree of renal insufficiency.

A variety of renal tubular disorders impair renal excretion of potassium. Children with pseudohypoaldosteronism type 1 have hyperkalemia, metabolic acidosis, and salt wasting leading to hypernatremia and volume depletion; aldosterone values are elevated. In the autosomal recessive variant, there is a defect in the renal sodium channel that is normally activated by aldosterone. Patients with this variant have severe symptoms, beginning in infancy. Patients with the autosomal dominant form have a defect in the aldosterone receptor, and the disease is milder, often remitting in adulthood. Pseudohypoaldosteronism type 2 (familial hyperkalemic hypertension), also called Gordon syndrome, is an autosomal dominant disorder characterized by hypertension caused by salt retention and impaired excretion of potassium and acid, leading to hyperkalemia and metabolic acidosis. Activating mutations in either WNK1 or WNK4, both serine-threonine kinases located in the distal nephron, cause Gordon syndrome. In the Bartter syndrome caused by

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**Table 55-4 Causes of Hyperkalemia**

<table>
<thead>
<tr>
<th>SPURIOUS LABORATORY VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemolysis</td>
</tr>
<tr>
<td>Tissue ischemia during blood drawing</td>
</tr>
<tr>
<td>Thrombocytosis</td>
</tr>
<tr>
<td>Leukocytosis</td>
</tr>
<tr>
<td>Familial pseudohyperkalemia (OMIM 609153/611184/612126)</td>
</tr>
</tbody>
</table>

**INCREASED INTAKE**

- Intravenous or oral
- Blood transfusions

**TRANSCELLULAR SHIFTS**

- Acidosis
- Rhabdomyolysis
- Tumor lysis syndrome
- Tissue necrosis
- Hemolysis/hematomas/gastrointestinal bleeding
- Succinylcholine
- Digitalis intoxication
- Fluoride intoxication
- β-Adrenergic blockers
- Exercise
- Hyperosmolality
- Insulin deficiency
- Malignant hyperthermia (OMIM 145600/601887)
- Hyperkalemic periodic paralysis (OMIM 170500)

**DECREASED EXCRETION**

- Renal failure
- Primary adrenal disease:
  - Acquired Addison disease
  - 21-Hydroxylase deficiency (OMIM 201910)
  - 3β-Hydroxysteroid dehydrogenase deficiency (OMIM 201810)
  - Lipoid congenital adrenal hyperplasia (OMIM 201710)
- Adrenal hypoplasia congenita (OMIM 300200)
- Aldosterone synthase deficiency (OMIM 203400/610600)
- Adrenoleukodystrophy (OMIM 300100)
- Hyporeninemic hypoaldosteronism:
  - Urinary tract obstruction
  - Sickle cell disease (OMIM 603903)
  - Kidney transplant
  - Lupus nephritis
- Renal tubular disease:
  - Pseudohypoaldosteronism type I (OMIM 264350/177735)
  - Pseudohypoaldosteronism type II (OMIM 145260)
  - Bartter syndrome, type 2 (OMIM 241200)
- Urinary tract obstruction
- Kidney transplant
- Medications:
  - Angiotensin-converting enzyme inhibitors
  - Angiotensin II blockers
  - Potassium-sparing diuretics
  - Calcineurin inhibitors
  - Nonsteroidal antiinflammatory drugs
  - Trimethoprim
  - Heparin
  - Drosperone (in some oral contraceptives)

**NOTE:**

- Table 55-4 includes causes of hyperkalemia that may be due to factors affecting laboratory measurement. These include hemolysis, tissue ischemia, and other causes, which may affect the measured potassium level but are not directly related to hyperkalemia. OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).
mutations in the potassium channel ROMK (type 2 Bartter syndrome), there can be transient hyperkalemia in neonates, but hypokalemia subsequently develops (see Chapter 531).

Acquired renal tubular dysfunction, with an impaired ability to excrete potassium, occurs in a number of conditions. These disorders, all characterized by tubulointerstitial disease, are often associated with impaired acid secretion and a secondary metabolic acidosis. In some affected children, the metabolic acidosis is the dominant feature, although a high potassium intake may unmask the defect in potassium handling. The tubular dysfunction can cause renal salt wasting, potentially leading to hyponatremia. Because of the tubulointerstitial damage, these conditions may also cause hyperkalemia as a result of hyporeninemic hypoaldosteronism.

The risk of hyperkalemia resulting from medications is greatest in patients with underlying renal insufficiency. The predominant mechanism of medication-induced hyperkalemia is impaired renal excretion, although angiotensin-converting enzyme inhibitors may worsen hyperkalemia in anuric patients, probably by inhibiting gastrointestinal potassium loss, which is normally upregulated in renal insufficiency. The hyperkalemia caused by trimethoprim generally occurs only at the very high doses used to treat Pneumocystis jiroveci pneumonia in patients with AIDS. Potassium-sparing diuretics may easily cause hyperkalemia, especially because they are often used in patients who are receiving oral potassium supplements. Oral contraceptives containing drospirenone, which blocks the action of aldosterone, may cause hyperkalemia and should not be used in patients with decreased renal function.

**Clinical Manifestations**

The most important effects of hyperkalemia are a result of the role of potassium in membrane polarization. The cardiac conduction system is usually the dominant concern. Changes in the electrocardiogram (ECG) begin with peaking of the T waves. This is followed, as the potassium level increases, by ST-segment depression, an increased PR interval, flattening of the P wave, and widening of the QRS complex. This process can eventually progress to ventricular fibrillation. Asystole may also occur. Some patients have paresthesias, fasciculations, weakness, and even an ascending paralysis, but cardiac toxicity usually precedes these clinical symptoms, emphasizing the danger of assuming that an absence of symptoms implies an absence of danger. Chronic hyperkalemia is generally better tolerated than acute hyperkalemia.

**DIAGNOSIS**

The etiology of hyperkalemia is often readily apparent. Spurious hyperkalemia is very common in children, so obtaining a second potassium measurement is often appropriate. If there is a significant elevation of the white blood cell or platelet count, the second measurement should be performed on a plasma sample that is evaluated promptly. The history should initially focus on potassium intake, risk factors for transcellular shifts of potassium, medications that cause hyperkalemia, and the presence of signs of renal insufficiency, such as oliguria and edema. Initial laboratory evaluation should include creatinine, BUN, and assessment of the acid–base status. Many etiologies of hyperkalemia cause a metabolic acidosis; a metabolic acidosis worsens hyperkalemia through the transcellular shift of potassium out of cells. Renal insufficiency is a common cause of the combination of metabolic acidosis and hyperkalemia. This association is also seen in diseases associated with aldosterone insufficiency or aldosterone resistance. Children with absence of or ineffective aldosterone often have hyponatremia and volume depletion because of salt wasting. Genetic diseases, such as congenital adrenal hyperplasia and pseudohypoaldosteronism, usually manifest in infancy and should be strongly considered in the infant with hyperkalemia and metabolic acidosis, especially if hyponatremia is present. It is important to consider the various etiologies of a transcellular shift of potassium. In some of these disorders, the potassium level continues to increase, despite the elimination of all potassium intake, especially when there is concurrent renal insufficiency. This increase is potentially seen in tumor lysis syndrome, hemolysis, rhabdomyolysis, and other causes of cell death. All of these entities can cause concomitant hyperphosphatemia and hyperuricemia. Rhabdomyolysis produces an elevated creatinine phosphokinase (CPK) value and hypocalcemia, whereas children with hemolysis have hemoglobinuria and a decreasing hematocrit. For the child with diabetes, an elevated blood glucose value suggests a transcellular shift of potassium.

**Treatment**

The plasma potassium level, the ECG, and the risk of the problem worsening determine the aggressiveness of the therapeutic approach. High serum potassium levels and the presence of ECG changes require vigorous treatment. An additional source of concern is the patient in whom plasma potassium levels are rising despite minimal intake. This situation can happen if there is cellular release of potassium (tumor lysis syndrome), especially in the setting of diminished excretion (renal failure).

The first action in a child with a concerning elevation of plasma potassium is to stop all sources of additional potassium (oral, intravenous). Washed red blood cells can be used for patients who require blood transfusions. If the potassium level is >6.5 mEq/L, an ECG should be obtained to help assess the urgency of the situation. Peak T waves are the first sign of hyperkalemia followed by a prolonged PR interval and, when most severe, a prolonged QRS complex. Life-threatening ventricular arrhythmias may also develop. The treatment of hyperkalemia has 2 basic goals: (a) to stabilize the heart to prevent life-threatening arrhythmias and (b) to remove potassium from the body. The treatments that acutely prevent arrhythmias all have the advantage of working quickly (within minutes) but do not remove potassium from the body. Calcium stabilizes the cell membrane of heart cells, preventing arrhythmias. It is given intravenously over a few minutes, and its action is almost immediate. Calcium should be given over 30 min in a patient who is receiving digitalis, because otherwise the calcium may cause arrhythmias. Bicarbonate causes potassium to move intracellularly, lowering the plasma potassium level. It is most efficacious in a patient with a metabolic acidosis. Insulin causes potassium to move intracellularly but must be given with glucose to avoid hypoglycemia. The combination of insulin and glucose works within 30 min. Nebulized albuterol, by stimulation of β1-receptors, leads to rapid intracellular movement of potassium. This has the advantage of not requiring an intravenous route of administration, allowing it to be given concurrently with the other measures.

It is critical to begin measures that remove potassium from the body. In patients who are not anuric, a loop diuretic increases renal excretion of potassium. A high dose may be required in a patient with significant renal insufficiency. Sodium polystyrene sulfonate (Kayexalate) is an exchange resin that is given either rectally or orally. Sodium in the resin is then excreted from the body. Some patients require dialysis for acute potassium removal. Dialysis is often necessary if the patient has either severe renal failure or an especially high rate of endogenous potassium release, as is sometimes present with tumor lysis syndrome or rhabdomyolysis. Hemodialysis rapidly lowers plasma potassium levels. Peritoneal dialysis is not nearly as quick or reliable, but it is usually adequate as long as the acute problem can be managed with medications and the endogenous release of potassium is not high.

Long-term management of hyperkalemia includes reducing intake via dietary changes and eliminating or reducing medications that cause hyperkalemia (see Chapter 535). Some patients require medications to increase potassium excretion, such as sodium polystyrene sulfonate and loop or thiazide diuretics. Some infants with chronic renal failure may need to start dialysis to allow adequate caloric intake without hyperkalemia. It is unusual for an older child to require dialysis principally to control chronic hyperkalemia. The disorders that are caused by a deficiency in aldosterone respond to replacement therapy with fludrocortisone.

**HYPOKALEMIA**

Hypokalemia is common in children, with most cases related to gastroenteritis.
Etiology and Pathophysiology

There are 4 basic mechanisms of hypokalemia (Table 55-5). Spurious hypokalemia occurs in patients with leukemia and very elevated white blood cell counts if plasma for analysis is left at room temperature, permitting the white blood cells to take up potassium from the plasma. With a transcellular shift, there is no change in total body potassium, although there may be concomitant potassium depletion resulting from other factors. Decreased intake, extrarenal losses, and renal losses are all associated with total body potassium depletion.

Because the intracellular potassium concentration is much higher than the plasma level, a significant amount of potassium can move into cells without markedly changing the intracellular potassium concentration. Alkalosis is one of the more common causes of a transcellular shift. The effect is much greater with a metabolic alkalosis than with a respiratory alkalosis. The impact of exogenous insulin on potassium movement into the cells is substantial in patients with diabetic ketoacidosis. Endogenous insulin may be the cause when a patient is given a bolus of glucose. Both endogenous (epinephrine in stress) and exogenous (albuterol) β-adrenergic agonists stimulate cellular uptake of potassium. Theophylline overdose, barium intoxication, administration of cesium chloride (a homeopathic cancer remedy), and toluene intoxication from paint or glue sniffing can cause a transcellular shift hypokalemia, often with severe clinical manifestations. Children with hypokalemic periodic paralysis, a rare autosomal dominant disorder, have acute cellular uptake of potassium (see Chapter 611). Thyrotoxic periodic paralysis, which is more common in Asians, is an unusual initial manifestation of hyperthyroidism. Affected patients have dramatic hypokalemia as a result of a transcellular shift of potassium. Hypokalemia can occur during refeeding syndrome (see Chapter 338.8).

Inadequate potassium intake occurs in anorexia nervosa; accompanying bulimia and laxative or diuretic abuse exacerbates the potassium deficiency. Sweat losses of potassium can be significant during vigorous exercise in a hot climate. Associated volume depletion and hyperaldosteronism increase renal losses of potassium (discussed later). Diarrhea fluid has a high concentration of potassium, and hypokalemia as a result of diarrhea is usually associated with a metabolic acidosis resulting from stool losses of bicarbonate. In contrast, a normal acid-base balance or a mild metabolic alkalosis is seen with laxative abuse. Intake of sodium polystyrene sulfonate or ingestion of clay because of its high potassium and sodium content can cause a transcellular shift of potassium 

<table>
<thead>
<tr>
<th>Table 55-5 Causes of Hypokalemia</th>
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<tbody>
<tr>
<td><strong>SPURIOUS</strong></td>
</tr>
<tr>
<td>High white blood cell count</td>
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<tr>
<td><strong>TRANSCELLULAR SHIFTS</strong></td>
</tr>
<tr>
<td>Alkalosis</td>
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<tr>
<td>Insulin</td>
</tr>
<tr>
<td>α-Adrenergic agonists</td>
</tr>
<tr>
<td>Drugs/toxins (theophylline, barium, toluene, cesium chloride, hydroxychloroquine)</td>
</tr>
<tr>
<td>Hypokalemic periodic paralysis (OMIM 170400)</td>
</tr>
<tr>
<td>Thyrotoxic period paralysis</td>
</tr>
<tr>
<td>Refeeding syndrome</td>
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<tr>
<td><strong>DECREASED INTAKE</strong></td>
</tr>
<tr>
<td>Anorexia nervosa</td>
</tr>
<tr>
<td><strong>EXTRARENAL LOSSES</strong></td>
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<tr>
<td>Diarrhea</td>
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<tr>
<td>Laxative abuse</td>
</tr>
<tr>
<td>Sweating</td>
</tr>
<tr>
<td>Sodium polystyrene sulfonate</td>
</tr>
<tr>
<td>Clay ingestion</td>
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<tr>
<td><strong>RENAL LOSSES</strong></td>
</tr>
<tr>
<td>With metabolic acidosis</td>
</tr>
<tr>
<td>Distal renal tubular acidosis (OMIM 179800/602722/267300)</td>
</tr>
<tr>
<td>Proximal renal tubular acidosis (OMIM 604278)*</td>
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<tr>
<td>Ureterosigmoidostomy</td>
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<tr>
<td>Diabetic ketoacidosis</td>
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<tr>
<td>Without specific acid–base disturbance</td>
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<tr>
<td>Tubular toxins: amphotericin, caplatin, aminoglycosides</td>
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<tr>
<td>Interstitial nephritis</td>
</tr>
<tr>
<td>Diuretic phase of acute tubular necrosis</td>
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<tr>
<td>Postobstructive diuresis</td>
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<tr>
<td>Hypomagnesemia</td>
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<tr>
<td>High urine anions (e.g., penicillin or penicillin derivatives)</td>
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<tr>
<td><strong>With metabolic alkalosis</strong></td>
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<tr>
<td>Low urine chloride</td>
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<tr>
<td>Emesis or nasogastric suction</td>
</tr>
<tr>
<td>Chloride-losing diarrhea (OMIM 214700)</td>
</tr>
<tr>
<td>Cystic fibrosis (OMIM 219700)</td>
</tr>
<tr>
<td>Low-chloride formula</td>
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<tr>
<td>Posthypercapnia</td>
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<tr>
<td>Previous loop or thiazide diuretic use</td>
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<tr>
<td>High urine chloride and normal blood pressure</td>
</tr>
<tr>
<td>Gitelman syndrome (OMIM 263800)</td>
</tr>
<tr>
<td>Bartter syndrome (OMIM 607364/602522/241200/601678)</td>
</tr>
<tr>
<td>Autosomal dominant hypoparathyroidism (OMIM 146200)</td>
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<tr>
<td>EAST syndrome (OMIM 612780)</td>
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<tr>
<td>Loop and thiazide diuretics</td>
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<tr>
<td>High urine chloride and high blood pressure</td>
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<tr>
<td>Adrenal adenoma or hyperplasia</td>
</tr>
<tr>
<td>Glucocorticoid-remediable aldosteronism (OMIM 103900)</td>
</tr>
<tr>
<td>Renovascular disease</td>
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<tr>
<td>Renin-secreting tumor</td>
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<tr>
<td>17β-Hydroxylase deficiency (OMIM 202110)</td>
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<td>11β-Hydroxylase deficiency (OMIM 202010)</td>
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<tr>
<td>Cushing syndrome</td>
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<tr>
<td>11β-Hydroxysteroid dehydrogenase deficiency (OMIM 218030)</td>
</tr>
<tr>
<td>Licorice ingestion</td>
</tr>
<tr>
<td>Liddle syndrome (OMIM 177200)</td>
</tr>
</tbody>
</table>

*Most cases of proximal renal tubular acidosis are not caused by this primary genetic disorder. Proximal renal tubular acidosis is usually part of Fanconi syndrome, which has multiple etiologies. EAST, epilepsy, ataxia, sensorineural hearing loss, and tubulopathy; OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).
were cases of chloride deficiency resulting from infant formula deficiency in chloride, which caused a metabolic alkalosis with hypokalemia and low urine chloride levels. Current infant formula is not deficient in chloride. A similar mechanism occurs in cystic fibrosis because of chloride loss in sweat. In congenital chloride-losing diarrhea, an autosomal recessive disorder, there is a high stool loss of chloride, leading to metabolic alkalosis, an unusual sequela of diarrhea. Because of stool potassium losses, chloride deficiency, and metabolic alkalosis, patients with this disorder have hypokalemia. During respiratory alkalosis, there is renal compensation, with retention of bicarbonate and excretion of chloride. After the respiratory acidosis is corrected, the patients have chloride deficiency and posthypercapnic alkalosis with secondary hypokalemia. Patients with chloride deficiency, metabolic alkalosis, and hypokalemia have a urinary chloride level of <10 mEq/L. Loop and thiazide diuretics lead to hypokalemia, metabolic alkalosis, and chloride deficiency. During treatment, these patients have high urine chloride levels resulting from the effect of the diuretic. However, after the diuretics are discontinued, there is residual chloride deficiency, the urinary chloride level is appropriately low, and neither the hypokalemia nor the alkalosis resolves until the chloride deficiency is corrected.

The combination of metabolic alkalosis, hypokalemia, a high urine chloride level, and normal blood pressure is characteristic of Bartter syndrome, Gitelman syndrome, and current diuretic use. Patients with any of these conditions have high urinary losses of potassium and chloride, despite a state of relative volume depletion with secondary hyperaldosteronism. Bartter and Gitelman syndromes are autosomal recessive disorders caused by defects in tubular transporters (see Chapter 531). Bartter syndrome is usually associated with hypercalciuria, and often with nephrocalcinosis, whereas children with Gitelman syndrome have low urinary calcium losses but hypomagnesemia as a consequence of urinary magnesium losses. Some patients with Bartter syndrome have hypomagnesemia.

Some patients with hypoparathyroidism and hypokalemia caused by an activating mutation of the calcium-sensing receptor (autosomal dominant hypoparathyroidism) have hypokalemia, hypomagnesemia, and metabolic alkalosis. The reason is that activation of the calcium-sensing receptor in the loop of Henle impairs tubular resorption of sodium and chloride, causing volume depletion and secondary hyperaldosteronism. EAST syndrome, an autosomal recessive disorder caused by mutations in the gene for a potassium channel present in the kidney, inner ear, and brain, consists of epilepsy, ataxia, sensorineural hearing loss, and tubulopathy (hypokalemia, metabolic alkalosis, hypomagnesemia, and hypocalciuria).

In the presence of high aldosterone levels, there is urinary loss of potassium, hypokalemia, metabolic alkalosis, and an elevated urinary chloride level. Also, renal retention of sodium leads to hypertension.

Primary hyperaldosteronism caused by adenoma or hyperplasia is much less common in children than in adults (see Chapter 578). Glucocorticoid-remediable aldosteronism, an autosomal dominant disorder that leads to high levels of aldosterone, is often diagnosed in childhood, although hypokalemia is not always present.

Increased aldosterone levels may be secondary to increased renin production. Renal artery stenosis leads to hypertension from increased renin and secondary hyperaldosteronism. The increased aldosterone can cause hypokalemia and metabolic alkalosis, although most patients have normal electrolyte levels. Renin-producing tumors, which are extremely rare, can cause hypokalemia.

A variety of disorders cause hypertension and hypokalemia without increased aldosterone levels. Some are a result of increased levels of mineralocorticoids other than aldosterone. Such increases occur in 2 forms of congenital adrenal hyperplasia (see Chapter 576). In 11β-hydroxylase deficiency, which is associated with virilization, the value of 11-deoxycorticosterone is elevated, causing variable hypertension and hypokalemia. A similar mechanism, increased 11-deoxycorticosterone, occurs in 17α-hydroxylase deficiency, but patients with this disorder are more uniformly hypertensive and hypokalemic, and they have a defect in sex hormone production. Cushing syndrome, frequently associated with hypertension, less commonly causes metabolic alkalosis and hypokalemia. This is secondary to the mineralocorticoid activity of cortisol. In 11β-hydroxysteroid dehydrogenase deficiency, an autosomal recessive disorder, the enzymatic defect prevents the conversion of cortisol to cortisone in the kidney. Because cortisol binds to and activates the aldosterone receptor, children with this deficiency have all the features of excessive mineralocorticoids, including hypertension, hypokalemia, and metabolic alkalosis. Patients with this disorder, which is also called apparent mineralocorticoid excess, respond to spironolactone therapy, which blocks the mineralocorticoid receptor. An acquired form of 11β-hydroxysteroid dehydrogenase deficiency occurs from the ingestion of substances that inhibit this enzyme. A classic example is glycyrrhizic acid, which is found in natural licorice. Liddle syndrome is an autosomal dominant disorder that results from an activating mutation of the distal nephron sodium channel that is normally upregulated by aldosterone. Patients have the characteristics of hyperaldosteronism—hypertension, hypokalemia, and alkalosis—but low serum aldosterone levels. These patients respond to the potassium-sparing diuretics (triaterene and amiloride) that inhibit this sodium channel (see Chapter 531.3).

**Clinical Manifestations**

The heart and skeletal muscle are especially vulnerable to hypokalemia. ECG changes include a flattened T wave, a depressed ST segment, and the appearance of a U wave, which is located between the T wave (if still visible) and the P wave. Ventricular fibrillation and torsades de points may occur, although usually only in the context of underlying heart disease. Hypokalemia makes the heart especially susceptible to digitalis-induced arrhythmias, such as supraventricular tachycardia, ventricular tachycardia, and heart block (see Chapter 435).

The clinical consequences of hypokalemia in skeletal muscle include muscle weakness and cramps. Paralysis is a possible complication, generally only at potassium levels <2.5 mEq/L. It usually starts in the legs and moves to the arms. Respiratory paralysis may require mechanical ventilation. Some patients have rhabdomyolysis; the risk increases with exercise. Hypokalemia slows gastrointestinal motility. This effect manifests as constipation; with potassium levels <2.5 mEq/L, an ileus may occur. Hypokalemia impairs bladder function, potentially leading to urinary retention.

Hypokalemia causes polyuria and polydipsia by impairing urinary concentrating ability, which produces nephrogenic diabetes insipidus. Hypokalemia stimulates renal ammonia production, an effect that is clinically significant if hepatic failure is present, because the liver cannot metabolize the ammonia. Consequently, hypokalemia may worsen hepatic encephalopathy. Chronic hypokalemia may cause kidney damage, including interstitial nephritis and renal cysts.

**Diagnosis**

Most causes of hypokalemia are readily apparent from the history. It is important to review the child’s diet, gastrointestinal losses, and medications. Both emesis and diuretic use can be surreptitious. The presence of hypertension suggests excess mineralocorticoids. Concomitant electrolyte abnormalities are useful clues. The combination of hypokalemia and metabolic acidosis is characteristic of diarrhea and of distal and proximal RTA. A concurrent metabolic alkalosis is characteristic of emesis or nasogastric losses, aldosterone excess, use of diuretics, and Bartter and Gitelman syndromes. Figure 55-5 shows an approach to persistent hypokalemia.

If a clear etiology is not apparent, the measurement of urinary potassium distinguishes between renal and extrarenal losses. The kidneys should conserve potassium in the presence of extrarenal losses. Urinary potassium losses can be assessed with a 24-hr urine collection, a spot potassium : creatinine ratio, a fractional excretion of potassium, or calculation of the transtubular potassium gradient (TTKG), which is the most widely used approach in children:

\[
\text{TTKG} = \frac{[K]_{\text{urine}}}{[K]_{\text{plasma}} \times (\text{plasma osmolality/urine osmolality})}
\]

where \([K]_{\text{urine}} = \text{urine potassium concentration}\) and \([K]_{\text{plasma}} = \text{plasma potassium concentration}\).
Part VII  Fluid and Electrolyte Disorders

The urine osmolality must be greater than the serum osmolality for the result of this calculation to be valid. A TTKG > 4 in the presence of hypokalemia suggests excessive urinary losses of potassium. The urinary potassium excretion value can be misleading if the stimulus for renal loss, such as a diuretic, is no longer present.

**Treatment**

Factors that influence the treatment of hypokalemia include the potassium level, clinical symptoms, renal function, the presence of transcellular shifts of potassium, ongoing losses, and the patient’s ability to tolerate oral potassium. Severe, symptomatic hypokalemia requires aggressive treatment. Supplementation is more cautious if renal function is decreased because of the kidney’s limited ability to excrete excessive potassium. The plasma potassium level does not always provide an accurate estimation of the total body potassium deficit because there may be shifts of potassium from the intracellular space to the plasma. Clinically, such shifts occur most commonly with metabolic acidosis and the insulin deficiency of diabetic ketoacidosis; the plasma potassium measurement underestimates the degree of total body potassium depletion. When these problems are corrected, potassium moves into the intracellular space, so more potassium supplementation is required to correct the hypokalemia. Likewise, the presence of a transcellular shift of potassium into the cells indicates that the total body potassium depletion is less severe. In an isolated transcellular shift, as occurs in hypokalemic periodic paralysis, potassium supplementation should be used cautiously.
given the risk of hyperkalemia when the transcellular shift resolves. This caution is especially required in thyrotoxic periodic paralysis, which responds dramatically to propranolol, with correction of weakness and hypokalemia. Patients who have ongoing losses of potassium need correction of the deficit and replacement of the ongoing losses.

Because of the risk of hyperkalemia, intravenous potassium should be used very cautiously. Oral potassium is safer, albeit not as rapid in urgent situations. Liquid preparations are bitter tasting; microencapsulated or wax matrix formulations are less irritating than tablets to the gastric mucosa (oral dose: 2-4 mEq/kg/day with a maximum of 120-240 mEq/day in divided doses). The dose of intravenous potassium is 0.5-1.0 mEq/kg, usually given over 1 hr. The adult maximum dose is 40 mEq. Conservative dosing is generally preferred. Potassium chloride is the usual choice for supplementation, although the presence of concurrent electrolyte abnormalities may dictate other options.

Patients with acidosis and hypokalemia can receive potassium acetate or potassium citrate. If hypophosphatemia is present, then some of the potassium deficit can be replaced with potassium phosphate. It is sometimes possible to decrease ongoing losses of potassium. For patients with excessive urinary losses, potassium-sparing diuretics are effective, but they need to be used cautiously in patients with renal insufficiency. If hypokalemia, metabolic alkalosis, and volume depletion are present (with gastric losses), then restoration of intravascular volume with adequate sodium chloride will decrease urinary potassium losses. Correction of concurrent hypomagnesemia is important because hypomagnesemia may cause hypokalemia. Disease-specific therapy is effective in many of the genetic tubular disorders.

Bibliography is available at Expert Consult.

## 55.5 Magnesium
Larry A. Greenbaum

### MAGNESIUM METABOLISM

#### Body Content and Physiologic Function

Magnesium is the fourth most common cation in the body and the third most common intracellular cation (see Fig. 55-3). Between 50% and 60% of body magnesium is in bone, where it serves as a reservoir because 30% is exchangeable, allowing movement to the extracellular space. Most intracellular magnesium is bound to proteins; only approximately 25% is exchangeable. Because cells with higher metabolic rates have higher magnesium concentrations, most intracellular magnesium is present in muscle and liver.

The normal plasma magnesium concentration is 1.5-2.3 mg/dL (1.2-1.9 mEq/L; 0.62-0.94 mmol/L), with some variation among clinical laboratories. Infants have slightly higher plasma magnesium concentrations than older children and adults. Only 1% of body magnesium is extracellular (60% ionized; 15% complexed; 25% protein bound). In the United States, serum magnesium is reported as mg/dL (Table 55-6).

Values in the left-column unit are converted into the right-column unit via multiplying by the conversion factor (e.g., calcium of 10 mg/dL × 0.25 = 2.5 mmol/L). Division of the right-column unit by the conversion factor converts to the units of the left-column unit.

Magnesium is a necessary cofactor for hundreds of enzymes. It is important for membrane stabilization and nerve conduction. Adenosine triphosphate (ATP) and guanosine triphosphate need associated magnesium when they are used by adenosine triphosphatases, cyclases, and kinases.

#### Intake

Between 30% and 50% of dietary magnesium is absorbed. Good dietary sources include green vegetables, cereals, nuts, meats, and hard water, although many foods contain magnesium. Human milk contains approximately 35 mg/L of magnesium; formula contains 40-70 mg/L. The small intestine is the major site of magnesium absorption, but the regulation of magnesium absorption is poorly understood. There is passive absorption, which permits high absorption in the presence of excessive intake. It probably occurs via a paracellular mechanism. Absorption is diminished in the presence of substances that complex with magnesium (free fatty acids, fiber, phytate, phosphate, oxalate); increased intestinal motility and calcium also decrease magnesium absorption. Vitamin D and parathyroid hormone (PTH) may enhance absorption, although this effect is limited. Intestinal absorption does increase when intake is decreased, possibly via a saturable active transport system. If there is no oral intake of magnesium, obligatory secretory losses prevent the complete elimination of intestinal losses.

#### Excretion

Renal excretion is the principal regulator of magnesium balance. There is no defined hormonal regulatory system, although PTH may increase tubular resorption. Approximately 15% of resorption occurs in the proximal tubule, and 70% in the thick ascending limb (TAL) of the loop of Henle. Proximal resorption may be higher in neonates. High serum magnesium levels inhibit resorption in the TAL, suggesting that active transport is involved. Approximately 5-10% of filtered magnesium is resorbed in the distal tubule. Hypomagnesemia increases absorption in the TAL and the distal tubule.

#### Hypomagnesemia

Hypomagnesemia is relatively common in hospitalized patients, although most cases are asymptomatic. Detection requires a high index of suspicion because magnesium is not measured in most basic metabolic panels.

#### Etiology and Pathophysiology

Gastrointestinal and renal losses are the major causes of hypomagnesemia (Table 55-7). Diarrheal fluid contains up to 200 mg/L of magnesium; gastric contents have only approximately 15 mg/L, but high losses can cause depletion. Steatorrhea causes magnesium loss as a result of the formation of magnesium-lipid salts; restriction of dietary fat can decrease losses.

**Hypomagnesemia with secondary hypocalcemia**, a rare autosomal recessive disorder, is caused by decreased intestinal absorption of magnesium and renal magnesium wasting. Patients with this disorder have mutations in a gene (TRPM6) that is expressed in intestine and kidney. TRPM6 codes for a transient receptor potential cation channel. The patients have seizures, tetany, tremor, or restlessness at 2-8 wk of life as a result of severe hypomagnesemia (0.2-0.8 mg/dL) and secondary hypocalcemia.

Renal losses may occur because of medications that are direct tubular toxins. Amphotericin frequently causes significant magnesium wasting and is typically associated with other tubular defects (especially potassium wasting). Cisplatin produces dramatic renal magnesium losses. Diuretics affect tubular handling of magnesium. Loop diuretics cause a mild increase in magnesium excretion, and thiazide diuretics have even less effect. Chronic use of proton pump inhibitors may cause hypomagnesemia. Potassium-sparing diuretics reduce magnesium losses. Osmostic agents, such as mannitol, glucose in diabetes

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**Table 55-6** Conversion Factors for Calcium, Magnesium, and Phosphorus

<table>
<thead>
<tr>
<th>UNIT</th>
<th>CONVERSION FACTOR</th>
<th>UNIT</th>
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</thead>
<tbody>
<tr>
<td>Calcium mg/dL</td>
<td>0.25</td>
<td>mmol/L</td>
</tr>
<tr>
<td>mEq/L</td>
<td>0.5</td>
<td>mmol/L</td>
</tr>
<tr>
<td>mEq/kg</td>
<td>0.5</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Magnesium mg/dL</td>
<td>0.411</td>
<td>mmol/L</td>
</tr>
<tr>
<td>mEq/L</td>
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<td>mmol/L</td>
</tr>
<tr>
<td>mEq/kg</td>
<td>0.822</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Phosphorus mg/dL</td>
<td>0.32</td>
<td>mmol/L</td>
</tr>
</tbody>
</table>
Bibliography


Causes of Hypomagnesemia

**GASTROINTESTINAL DISORDERS**
- Diarrhea
- Nasogastric suction or emesis
- Inflammatory bowel disease
- Celiac disease
- Cystic fibrosis
- Intestinal lymphangiectasia
- Small bowel resection or bypass
- Pancreatitis
- Protein-calorie malnutrition
- Hypomagnesemia with secondary hypocalcemia (OMIM 602014)*

**RENNAL DISORDERS**
- Medications
  - Amphotericin
  - Cisplatin
  - Cyclosporin
  - Loop diuretics
  - Mannitol
  - Pentamidine
  - Proton pump inhibitors
  - Aminoglycosides
- Thiazide diuretics
- Epidermal growth factor receptor inhibitors
- Diabetes
- Acute tubular necrosis (recovery phase)
- Postobstructive nephropathy
- Chronic kidney diseases
- Intersitial nephritis
- Glomerulonephritis
- Post-renal transplantation
- Hypercalcemia
- Intravenous fluids
- Primary aldosteronism
- Genetic diseases
  - Gitelman syndrome (OMIM 263800)
  - Bartter syndrome (OMIM 607364/601678)
  - Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (OMIM 248250)
  - Familial hypomagnesemia with hypercalciuria, nephrocalcinosis, and severe ocular involvement (OMIM 248190)
  - Autosomal recessive renal magnesium wasting with normocalciuria (OMIM 611718)
  - Renal cysts and diabetes syndrome (OMIM 137920)
  - Autosomal dominant hypomagnesemia (OMIM 160120/613882/154020)
  - EAST syndrome (OMIM 612780)
  - Autosomal dominant hypoparathyroidism (OMIM 146200)
  - Mitochondrial disorders (OMIM 500005)

**MISCELLANEOUS CAUSES**
- Poor intake
- Hungry bone syndrome
- Insulin administration
- Pancreatitis
- Intrauterine growth retardation
- Infants of diabetic mothers
- Exchange transfusion

A number of rare genetic diseases cause renal magnesium loss. **Gitelman and Bartter syndromes**, both autosomal recessive disorders, are the most common entities (see Chapter 531). Gitelman syndrome, which is caused by a defect in the thiazide-sensitive Na⁺/Cl⁻ cotransporter in the distal tubule, is usually associated with hypomagnesemia. Hypomagnesemia occurs in a minority of patients with Bartter syndrome, which can be caused by mutations in multiple genes that are necessary for sodium and chloride reabsorption in the loop of Henle. In both disorders, there is hypokalemic metabolic alkalosis. Typically, hypomagnesemia is not severe and is asymptomatic, although tetany as a result of hypomagnesemia occasionally occurs.

**Familial hypomagnesemia with hypercalciuria and nephrocalcinosis** (Michelis-Castrillo syndrome), an autosomal recessive disorder, is caused by mutations in the gene for claudin 16 (paracellin-1), which is located in the tight junctions of the TAL of the loop of Henle. Patients with the disease have severe renal wasting of magnesium and calcium with secondary hypomagnesemia and nephrocalcinosis; serum calcium levels are normal. Chronic renal failure frequently occurs during childhood. Other features include kidney stones, urinary tract infections, hematuria, increased PTH levels, tetany, seizures, incomplete distal RTA, hyperuricemia, polycystic kidney disease, and polydipsia. Patients with familial hypomagnesemia with hypercalciuria, nephrocalcinosis, and severe ocular involvement have mutations in the gene for claudin 19.

**Autosomal recessive renal magnesium wasting with normocalciuria** is caused by mutations in the epidermal growth factor gene. Clinical manifestations include seizures, mild to moderate psychomotor retardation, and brisk tendon reflexes.

**Autosomal dominant renal magnesium wasting** is caused by mutations in a number of different genes. A dominant-negative mutation in the gene encoding the Na⁺,K⁺-adenosine triphosphatase γ subunit is associated with hypomagnesemia, increased urinary magnesium losses, hypercalciuria, and normocalcemia. Patients may present with seizures; most are asymptomatic, despite serum magnesium levels of 0.8-1.5 mg/dL. Mutations in CNNM2, which encodes a protein that mediates magnesium-sensitive sodium currents, cause isolated hypomagnesemia. A mutation in KCNA1, a gene that encodes a potassium channel, also causes an autosomal dominant form of hypomagnesemia; symptoms may be severe.

**Renal cysts and diabetes syndrome**, which is caused by mutations in the gene for hepatocyte nuclear factor-1β, is associated with hypomagnesemia, despite the frequent presence of renal insufficiency. The hypomagnesemia is usually mild but may cause symptomatic hypocalcemia. **EAST syndrome** is caused by mutations in a potassium channel, and patients with this autosomal recessive disorder have hypokalemia, metabolic alkalosis, and hypomagnesemia. **Autosomal dominant hypoparathyroidism** is caused by an activating mutation in the calcium-sensing receptor, which also senses magnesium levels in the kidney (see Chapter 571). The mutated receptor inappropriately perceives that magnesium and calcium levels are elevated, leading to urinary wasting of both cations. Hypomagnesemia, if present, is usually mild. A mutation in a mitochondrially encoded transfer RNA is associated with hypomagnesemia, hypertension, and hypercholesterolemia. Hypomagnesemia is occasionally present in children with other mitochondrial disorders.

Poor intake is an unusual cause of hypomagnesemia, although it can be seen in children who are hospitalized and receive only intravenous fluids without magnesium. In **hungry bone syndrome**, which most frequently occurs after parathyroidectomy in patients with hyperparathyroidism, magnesium moves into bone as a result of accelerated bone formation. These patients usually have hypocalcemia and hypophosphatemia via the same mechanism. A similar mechanism can occur during the refedding phase of protein-calorie malnutrition in children, with high magnesium use during cell growth depleting the patient’s limited reserves. Insulin therapy stimulates uptake of magnesium by cells, and in diabetic ketoacidosis, in which total body magnesium is low because of osmotic losses, hypomagnesemia frequently occurs. In **pancreatitis**, there is saponification of magnesium and calcium in necrotic fat, causing both hypomagnesemia and hypocalcemia.

*This disorder is also associated with renal magnesium wasting.

**EAST**, epilepsy, ataxia, sensorineural hearing loss, and tubulopathy,
Transient hypomagnesemia in newborns, which is sometimes idiopathic, is more commonly seen in infants of diabetic mothers, presumably as a result of maternal depletion from osmotic losses. Other maternal diseases that cause magnesium losses predispose infants to hypomagnesemia. Hypomagnesemia is more common in infants with intraperineal growth restriction. Hypomagnesemia may develop in newborn infants who require exchange transfusions because of magnesium removal by the citrate in banked blood.

Clinical Manifestations
Hypomagnesemia causes secondary hypocalcemia by impairing the release of PTH by the parathyroid gland and through blunting of the tissue response to PTH. Thus, hypomagnesemia is part of the differential diagnosis of hypocalcemia (see Chapter 57). It usually occurs only at magnesium levels <0.7 mg/dL. The dominant manifestations of hypomagnesemia are caused by hypocalcemia: tetany, presence of Chvostek and Trousseau signs, and seizures. However, with severe hypomagnesemia, these same signs and symptoms may be present despite normocalcemia. Persistent hypocalcemia caused by hypomagnesemia is a rare cause of rickets.

Many causes of hypomagnesemia also result in hypokalemia. Hypomagnesemia may produce renal potassium wasting and hypokalemia that corrects only with magnesium therapy. ECG changes with hypomagnesemia include flattening of the T wave and lengthening of the ST segment. Arrhythmias may occur, almost always in the setting of underlying heart disease.

Diagnosis
The etiology of hypomagnesemia is often readily apparent from the clinical situation. The child should be assessed for gastrointestinal disease, adequate intake, and kidney disease, with close attention paid to medications that may cause renal magnesium wasting. When the diagnosis is uncertain, an evaluation of urinary magnesium losses distinguishes between renal and nonrenal causes. The fractional excretion of magnesium (FE_Mg) is calculated via the following formula:

\[
FE_{Mg} = \frac{U_{Mg} \times P_{Cr}}{P_{Mg} \times U_{Cr}} \times 100
\]

where \( U_{Mg} \) is urinary magnesium concentration, \( P_{Cr} \) is plasma creatinine concentration, \( P_{Mg} \) is plasma magnesium concentration, and \( U_{Cr} \) is urinary magnesium concentration. The plasma magnesium concentration is multiplied by 0.7 because approximately 30% is bound to albumin and not filtered at the glomerulus.

The \( FE_{Mg} \) does not vary with age, but it does change according to the serum magnesium concentration. The \( FE_{Mg} \) ranges from 1-8% in children with normal magnesium levels. In the presence of hypomagnesemia as a result of extrarenal causes, it should be low because of renal conservation, typically <2%. The \( FE_{Mg} \) is inappropriately elevated in the setting of renal magnesium wasting; values are usually >4% and frequently >10%. The measurement should not be made during a magnesium infusion, because the acute increase in serum magnesium increases urinary magnesium. Other approaches for evaluating urinary magnesium losses include calculation of 24 hr urinary magnesium losses and of the ratio of urine magnesium:urine creatinine, both of which vary with age.

The genetic causes of renal magnesium loss are distinguished on the basis of the measurement of other serum and urinary electrolytes. Children with Gitelman and Bartter syndromes have hypokalemia and metabolic alkalosis.

Treatment
Severe hypomagnesemia is treated with parenteral magnesium. Magnesium sulfate is given at a dose of 25-50 mg/kg (0.05-0.1 mL/kg of a 50% solution; 2.5-5.0 mg/kg of elemental magnesium). It is administered as a slow intravenous infusion, although it may be given intramuscularly in neonates. The rate of intravenous infusion should be slowed if a patient experiences diaphoresis, flushing, or a warm sensation. The dose is often repeated every 6 hr (every 8-12 hr in neonates), for a total of 2-3 doses, before the plasma magnesium concentration is rechecked. Lower doses are used in children with renal insufficiency.

Long-term therapy is usually given orally. Preparations include magnesium gluconate (5.4 mg elemental magnesium/100 mg), magnesium oxide (60 mg elemental magnesium/100 mg), and magnesium sulfate (10 mg elemental magnesium/100 mg). There are sustained-released preparations, such as Slow-Mag (60 mg elemental magnesium/tablet) and Mag-Tab SR (84 mg elemental magnesium/tablet). Oral magnesium dosing should be divided to decrease cathartic side effects. Alternatively, oral magnesium are intramuscular injections and nighttime nasogastric infusion, both designed to minimize diarrhea. Magnesium supplementation must be used cautiously in the context of renal insufficiency.

HYPERMAGNESEMIA
Clinically significant hypermagnesemia is almost always secondary to excessive intake. It is unusual, except in neonates born to mothers who are receiving intravenous magnesium for preeclampsia or eclampsia (see Chapter 106).

Etiology and Pathophysiology
There is no feedback mechanism to prevent magnesium absorption from the gastrointestinal tract. Magnesium is present in high amounts in certain laxatives, enemas, cathartics used to treat drug overdoses, and antacids. It is also usually present in total parenteral nutrition, and neonates may receive high amounts transplacently if maternal levels are elevated. Usually the kidneys excrete excessive magnesium, but this ability is diminished in patients with chronic renal failure. In addition, neonates and young infants are vulnerable to excessive magnesium ingestion because of their reduced GFR. Most pediatric cases not related to maternal hypermagnesemia occur in infants as a result of excessive use of antacids or laxatives. Mild hypermagnesemia may occur in chronic renal failure, familial hypocalciuric hypercalcemia, diabetic ketoacidosis, lithium ingestion, milk-alkali syndrome, and tumor lysis syndrome. The hypermagnesemia in diabetic ketoacidosis occurs despite significant intracellular magnesium depletion as a result of urinary losses; hypomagnesemia often occurs after insulin treatment.

Clinical Manifestations
Symptoms usually do not appear until the plasma magnesium level is >4.5 mg/dL. Hypermagnesemia inhibits acetylcholine release at the neuromuscular junction, producing hypotonia, hyporeflexia, and weakness; paralysis occurs at high concentrations. The neuromuscular effects may be exacerbated by aminoglycoside antibiotics. Direct CNS depression causes lethargy and sleepiness; infants have a poor suck. Elevated magnesium values are associated with hypotension because of vascular dilation, which also causes flushing. Hypotension can be profound at higher concentrations from a direct effect on cardiac function. ECG changes include prolonged PR, QRS, and QT intervals. Severe hypermagnesemia (>15 mg/dL) causes complete heart block and cardiac arrest. Other manifestations of hypermagnesemia include nausea, vomiting, and hypocalcemia.

Diagnosis
Except for the case of the neonate with transplacental exposure, a high index of suspicion and a good history are necessary to make the diagnosis of hypermagnesemia. Prevention is essential; magnesium-containing compounds should be used judiciously in children with renal insufficiency.

Treatment
Most patients with normal renal function rapidly clear excessive magnesium. Intravenous hydration and loop diuretics can accelerate this process. In severe cases, especially in patients with underlying renal insufficiency, dialysis may be necessary. Hemodialysis works faster than peritoneal dialysis. Exchange transfusion is another option in newborn infants. Supportive care includes monitoring of cardiorespiratory status, provision of fluids, monitoring of electrolyte levels, and
Approximately 65% of plasma phosphorus is in phospholipids, but these compounds are insoluble in acid and are not measured by clinical laboratories. It is the phosphorus content of plasma phosphate that is determined. The result is reported as either phosphate or phosphorus, although even when the term phosphate is used, it is actually the phosphorus concentration that is measured and reported. The result is that the terms phosphate and phosphorus are often used interchangeably. The term phosphorus is preferred when one is referring to the plasma concentration. Conversion from the units used in the United States (mg/dL) to mmol/L is straightforward (see Table 55-6).

**PHOSPHORUS METABOLISM**

**Body Content and Physiologic Function**

Most phosphorus is in bone or is intracellular, with <1% in plasma. At a physiologic pH, there are monovalent and divalent forms of phosphate because the pK of these forms is 6.8. Approximately 80% is divalent, and the remainder is monovalent at a pH of 7.4. A small percentage of plasma phosphate, approximately 15%, is protein bound. The remainder can be filtered by the glomerulus, with most existing as free phosphate and a small percentage complexed with calcium, magnesium, or sodium. Phosphate is the most plentiful intracellular anion, although the majority is part of a larger compound (ATP).

More than that of any other electrolyte, the phosphate concentration varies with age (Table 55-8). The teleologic explanation for the high concentration during childhood is the need for phosphorus to facilitate growth. There is diurnal variation in the plasma phosphorus concentration, with the peak during sleep.

Phosphorus, as a component of ATP and other trinucleotides, is critical for cellular energy metabolism. It is necessary for cell signaling and nucleic acid synthesis, and it is a component of cell membranes and other structures. Along with calcium, phosphorus is necessary for skeletal mineralization. There is a significant need for a net positive phosphorus balance during growth, with the growing skeleton especially vulnerable to deficiency.

**Intake**

Phosphorus is readily available in food. Milk and milk products are the best sources of phosphorus; high concentrations are present in meat and fish. Vegetables have more phosphorus than fruits and grains. Gastrointestinal absorption of phosphorus is fairly proportional to intake, with approximately 65% of intake being absorbed, including a small amount that is secreted. Absorption, almost exclusively in the small intestine, occurs via a paracellular diffusive process and a vitamin D-regulated transcellular pathway. However, the impact of the change in phosphorus absorption caused by vitamin D is relatively small compared with the effect of variations in phosphorus intake.

**Excretion**

Despite the wide variation in phosphorus absorption dictated by oral intake, excretion matches intake, except for the needs for growth. The kidney regulates phosphorus balance, which is determined by intrarenal mechanisms and hormonal actions on the nephron.

Approximately 90% of plasma phosphate is filtered at the glomerulus, although there is some variation based on plasma phosphate and calcium concentrations. There is no significant secretion of phosphate along the nephron. Resorption of phosphate occurs mostly in the proximal tubule, although a small amount can be resorbed in the distal tubule. Normally, approximately 85% of the filtered load is resorbed.

A sodium-phosphate cotransporter mediates the uptake of phosphate into the cells of the proximal tubule.

The dietary phosphorus determines the amount of phosphate resorbed by the nephron. There are both acute and chronic changes in phosphate resorption that are based on intake. Many of these changes appear to be mediated by intrarenal mechanisms that are independent of regulatory hormones. Fibroblast growth factor-23 (FGF-23) inhibits renal resorption of phosphorus in the proximal tubule, and its level increases in the setting of hyperphosphatemia. FGF-23 also inhibits synthesis of calcitriol in the kidney by decreasing 1α-hydroxylase activity.

PTh, which is secreted in response to a low plasma calcium level, decreases resorption of phosphate, increasing the urinary phosphate level. This process appears to have a minimal effect during normal physiologic variation in PTh levels. However, it does have an impact in the setting of pathologic changes in PTh synthesis.

Low plasma phosphorus stimulates the 1α-hydroxylase in the kidney that converts 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (calcitriol). Calcitriol increases intestinal absorption of phosphorus and is necessary for maximal renal resorption of phosphate. The effect of a change in calcitriol on urinary phosphate is significant only when the level of calcitriol was initially low, arguing against a role for calcitriol in nonpathologic conditions.

**HYPOPHOSPHATEMIA**

Because of the wide variation in normal plasma phosphorus levels, the definition of hypophosphatemia is age-dependent (see Table 55-8). The normal range reported by a laboratory may be based on adult normal values and, therefore, may be misleading in children. A serum phosphorus level of 3 mg/dL, a normal value in an adult, indicates clinically significant hypophosphatemia in an infant.

The plasma phosphorus level does not always reflect the total body stores because only 1% of phosphorus is extracellular. Thus, a child may have significant phosphorus deficiency despite a normal plasma phosphorus concentration. This situation is especially common in conditions in which there is a shift of phosphorus from the intracellular space.

**Etiology and Pathophysiology**

A variety of mechanisms cause hypophosphatemia (Table 55-9). A transcellular shift of phosphorus into cells occurs with processes that stimulate cellular usage of phosphorus (glycolysis). Usually, this shift causes only a minor, transient decrease in plasma phosphorus, but if intracellular phosphorus deficiency is present, the plasma phosphorus level can decrease significantly, producing symptoms of acute hypophosphatemia. Glucose infusion stimulates insulin release, leading to entry of glucose and phosphorus into the cells. Phosphorus is then used during glycolysis and other metabolic processes. A similar phenomenon can occur during the treatment of diabetic ketoacidosis, and patients with this disorder are typically phosphorus-depleted owing to urinary phosphorus losses. Refeeding of patients with protein-calorie malnutrition causes anabolism, which leads to significant cellular demand for phosphorus. The increased phosphorus uptake for incorporation into newly synthesized compounds containing phosphorus leads to hypophosphatemia, which can be severe and symptomatic. Refeeding hypophosphatemia occurs frequently during treatment of severe anorexia nervosa. It can occur during treatment of children with malnutrition from any cause, such as cystic fibrosis, Crohn

<table>
<thead>
<tr>
<th>Table 55-8</th>
<th>Serum Phosphorus Levels During Childhood</th>
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<tr>
<td>AGE</td>
<td>PHOSPHORUS LEVEL (mg/dL)</td>
</tr>
<tr>
<td>0-5 day</td>
<td>4.8-8.2</td>
</tr>
<tr>
<td>1-3 yr</td>
<td>3.8-6.5</td>
</tr>
<tr>
<td>4-11 yr</td>
<td>3.7-5.6</td>
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<tr>
<td>12-15 yr</td>
<td>2.9-5.4</td>
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<tr>
<td>16-19 yr</td>
<td>2.7-4.7</td>
</tr>
</tbody>
</table>

Bibliography is available at Expert Consult.
Bibliography
honesty. Very-low-birthweight infants have particularly rapid skeletal growth, and phosphorus deficiency and rickets may develop if they are fed human milk or formula for term infants. There is also a relative deficiency of calcium. The provision of additional calcium and phosphorus, using breast milk fortifier or special premature infant formula, prevents this complication. Phosphorus deficiency, sometimes with concomitant calcium and vitamin D deficiencies, occurs in infants who are not given enough milk or who receive a milk substitute that is nutritionally inadequate.

Antacids containing aluminum hydroxide, such as Maalox and Mylanta, bind dietary phosphorus and secreted phosphorus, preventing absorption. This process can cause phosphorus deficiency and rickets in growing children. A similar mechanism causes hypophosphatemia in patients who are overtreated for hyperphosphatemia with phosphorus binders. In children with kidney failure, the addition of dialysis to phosphorus binders increases the risk of iatrogenic hypophosphatemia in these normally hyperphosphatemic patients. This complication, which is more common in infants, can worsen renal osteodystrophy.

Excessive renal losses of phosphorus occur in a variety of inherited and acquired disorders. Because PTH inhibits the resorption of phosphorus in the proximal tubule, hyperparathyroidism causes hypophosphatemia (see Chapter 53). The dominant clinical manifestation, however, is hypercalcemia, and the hypophosphatemia is usually asymptomatic. The phosphorus level in hyperparathyroidism is not extremely low, and there is no continued loss of phosphorus because a new steady state is achieved at the lower plasma phosphorus level. Renal excretion, therefore, does not exceed intake over the long-term. There are occasional malignancies that produce PTH-related peptide, which has the same actions as PTH and causes hypophosphatemia and hypercalcemia.

A variety of diseases cause renal phosphate wasting, hypophosphatemia, and rickets resulting from excess FGF-23 (see Chapter 51). These disorders include X-linked hypophosphatemic rickets, tumors induced osteomalacia, autosomal dominant hypophosphatemic rickets, and autosomal recessive hypophosphatemic rickets. Heterozygous mutations in a phosphate transporter or a regulator of proximal rickets, and nephro lithiasis resulting from excess FGF-23 (see Chapter 51). The clinical sequelae are a result of the metabolic acidosis and hypophosphatemia. In children, an underlying genetic disease, most commonly cystinosis, often causes Fanconi syndrome, but it can be secondary to a variety of toxins and acquired diseases. Some patients have incomplete Fanconi syndrome, and phosphorus wasting may be one of the manifestations.

Dent disease, an X-linked disorder, can cause renal phosphorus wasting and hypophosphatemia, although the latter is not present in most cases. Other possible manifestations of Dent disease include tubular proteinuria, hypercalcuria, nephrolithiasis, rickets, and chronic renal failure. Dent disease may be secondary to mutations in a gene that encodes a chloride channel or the OCRL1 gene, which may also cause Lowe syndrome (see Chapter 529.1). Hypophosphatemic rickets with hypercalciuria is a rare disorder, principally described in kindreds from the Middle East. Mutations in a sodium-phosphate cotransporter cause hypophosphatemia in this disorder, and complications may include nephrolithiasis and osteoporosis; the disorder is autosomal dominant.

Metabolic acidosis inhibits resorption of phosphorus in the proximal tubule. In addition, metabolic acidosis causes a transcellular shift of phosphorus out of cells because of intracellular catabolism. This

<table>
<thead>
<tr>
<th>Table 55-9 Causes of Hypophosphatemia</th>
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<tr>
<td><strong>TRANSCELLULAR SHIFTS</strong></td>
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<tr>
<td>Glucose infusion</td>
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<td>Refeeding</td>
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<td>Parathyroid hormone–related peptide</td>
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<tr>
<td>X-linked hypophosphatemic rickets (OMIM 307800)</td>
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<td>Overproduction of fibroblast growth factor-23</td>
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<td>Tumor-induced rickets</td>
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<td>McCune-Albright syndrome</td>
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<td>Fanconi syndrome</td>
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<td>Dent disease (OMIM 300009/300555)</td>
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<td>Hypophosphatemic rickets with hypercalciuria (OMIM 241530)</td>
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<td>Volume expansion and intravenous fluids</td>
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<td>Vitamin D–dependent rickets type 1 (OMIM 264700)</td>
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<td>Vitamin D–dependent rickets type 2 (OMIM 277440)</td>
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<td>Dialysis</td>
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released phosphorus is subsequently lost in the urine, leading to significant phosphorus depletion, even though the plasma phosphorus level may be normal. This classically occurs in diabetic ketoacidosis in which renal phosphorus loss is further increased by the osmotic diuresis. With correction of the metabolic acidosis and the administration of insulin, both of which cause a transcellular movement of phosphorus into the cells, there is a marked decrease in the plasma phosphorus level.

Volume expansion from any cause, such as hyperaldosteronism or SIADH, inhibits resorption of phosphorus in the proximal tubule. This effect also occurs with high rates of intravenous fluids. Thiazide and loop diuretics can increase renal phosphorus excretion, but the increase is seldom clinically significant. Glycosuria and glucocorticoids inhibit renal conservation of phosphorus. Hypophosphatemia is common after kidney transplantation as a result of urinary phosphorus losses. Possible explanations include preexisting secondary hyperparathyroidism from chronic renal failure, glucocorticoid therapy, and upregulation of FGF-23 before transplantation. The hypophosphatemia usually resolves in a few months.

Both acquired and genetic causes of vitamin D deficiency are associated with hypophosphatemia (see Chapter 51). The pathogenesis is multifactorial. Vitamin D deficiency, by impairing intestinal calcium absorption, causes secondary hyperparathyroidism that leads to increased urinary phosphorus wasting. An absence of vitamin D decreases intestinal absorption of phosphorus and directly decreases renal resorption of phosphorus. The dominant clinical manifestation is rickets, although some patients have muscle weakness that may be related to phosphorus deficiency.

Alcoholism is the most common cause of severe hypophosphatemia in adults. Fortunately, many of the risk factors that predispose adult alcoholics to hypophosphatemia are not usually present in adolescents (malnutrition, antacid abuse, recurrent episodes of diabetic ketoacidosis). Hypophosphatemia often occurs in sepsis, but the mechanism is not clear. Aggressive, protracted hemodialysis, as might be used for the treatment of methanol or ethylene glycol ingestion, can cause hypophosphatemia.

Clinical Manifestations
There are acute and chronic manifestations of hypophosphatemia. Rickets occurs in children with long-term phosphorus deficiency. The clinical features of rickets are described in Chapter 51.

Severe hypophosphatemia, typically at levels <1.0-1.5 mg/dL, may affect every organ in the body because phosphorus has a critical role in maintaining adequate cellular energy. Phosphorus is a component of ATP and is necessary for glycolysis. With inadequate phosphorus, red blood cell 2,3-diphosphoglycerate levels decrease, impairing release of oxygen to the tissues. Severe hypophosphatemia can cause hemolysis and dysfunction of white blood cells. Chronic hypophosphatemia causes proximal muscle weakness and atrophy. In the intensive care unit, phosphorus deficiency may slow weaning from mechanical ventilation or cause acute respiratory failure. Rhabdomyolysis is the most common complication of acute hypophosphatemia, usually in the setting of an acute transcellular shift of phosphorus into cells in a child with chronic phosphorus depletion (anorexia nervosa). The rhabdomyolysis is actually somewhat protective, in that there is cellular release of phosphorus. Other manifestations of severe hypophosphatemia include cardiac dysfunction and neurologic symptoms, such as tremor, paresthesia, ataxia, seizures, delirium, and coma.

Diagnosis
The history and basic laboratory evaluation often suggest the etiology of hypophosphatemia. The history should investigate nutrition, medications, and familial disease. Hypophosphatemia and rickets in an otherwise healthy young child suggests a genetic defect in renal phosphorus conservation, Fanconi syndrome, inappropriate use of antacids, poor nutrition, vitamin D deficiency, or a genetic defect in vitamin D metabolism. The patient with Fanconi syndrome usually has metabolic acidosis, glycosuria, aminoaciduria, and a low plasma uric acid level. Measurement of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D, calcium, and PTH differentiates among the various vitamin D deficiency disorders and primary renal phosphate wasting (see Chapter 51). Hyperparathyroidism is easily distinguished by the presence of elevated plasma PTH and calcium values.

Treatment
The plasma phosphorus level, the presence of symptoms, the likelihood of chronic depletion, and the presence of ongoing losses dictate the approach to therapy. Mild hypophosphatemia does not require treatment unless the clinical situation suggests that chronic phosphorus depletion is present or that losses are ongoing. Oral phosphorus can cause diarrhea, so the doses should be divided. Intravenous therapy is effective in patients who have severe deficiency or who cannot tolerate oral medications. Intravenous phosphorus is available as either sodium phosphate or potassium phosphate, with the choice usually based on the patient's plasma potassium level. Starting doses are 0.08-0.16 mmol/kg over 6 hr. The oral preparations of phosphorus are available with various ratios of sodium and potassium. This is an important consideration because some patients may not tolerate the potassium load, whereas supplemental potassium may be helpful in some diseases, such as Fanconi syndrome and malnutrition. Oral maintenance dosages are 2-3 mmol/kg/day in divided doses.

Increasing dietary phosphorus is the only intervention needed in infants with inadequate intake. Other patients may also benefit from increased dietary phosphorus, usually from dairy products. Phosphorus-binding antacids should be discontinued in patients with hypophosphatemia. Certain diseases require specific therapy (see Chapter 51).

HYPERPHOSPHATEMIA

Etiology and Pathophysiology
Renal insufficiency is the most common cause of hyperphosphatemia, with the severity proportional to the degree of kidney impairment (see Chapter 535). This occurs because gastrointestinal absorption of the large dietary intake of phosphorus is unregulated, and the kidneys normally excrete this phosphorus. As renal function deteriorates, increased excretion of phosphorus is able to compensate. When kidney function is <30% of normal, hyperphosphatemia usually develops, although the time of its development may vary considerably according to dietary phosphorus absorption. Many of the other causes of hyperphosphatemia are more likely to develop in the setting of renal insufficiency (Table 55-10).

Cellular content of phosphorus is high relative to plasma phosphorus, and cell lysis can release substantial phosphorus. This is the etiology of hyperphosphatemia in tumor lysis syndrome, rhabdomyolysis, and acute hemolysis. These disorders cause concomitant potassium

<table>
<thead>
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<th>Table 55-10</th>
<th>Causes of Hyperphosphatemia</th>
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<td><strong>TRANSCELLULAR SHIFTS</strong></td>
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<td>Rhabdomyolysis</td>
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<td>Acute hemolysis</td>
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<td>Cow's milk in infants</td>
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<td>Treatment of hypophosphatemia</td>
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<td>Vitamin D intoxication</td>
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<td><strong>DECREASED EXCRETION</strong></td>
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<td>Hyperparathyroidism or pseudohyperparathyroidism (OMIM 146200/603233/103580/241410/203330)</td>
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<td>Hyperthyroidism</td>
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<td>Tumoral calcinosis with hyperphosphatemia (OMIM 211900)</td>
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release and the risk of hyperkalemia. Additional features of tumor lysis and rhabdomyolysis are hyperuricemia and hypocalcemia, whereas indirect hyperbilirubinemia and elevated lactate dehydrogenase values are often present with hemolysis. An elevated CPK level is suggestive of rhabdomyolysis. During lactic acidosis or diabetic ketoacidosis, usage of phosphorus by cells decreases, and phosphorus shifts into the extracellular space. This problem reverses when the underlying problem is corrected, and especially with diabetic ketoacidosis, patients subsequently become hypophosphatemic as a result of previous renal phosphorus loss.

Excessive intake of phosphorus is especially dangerous in children with renal insufficiency. Neonates are at risk because renal function is normally reduced during the 1st few months of life. In addition, they may erroneously be given doses of phosphorus that are meant for an older child or adult. In infants fed cow’s milk, which has higher phosphorus content than breast milk or formula, hyperphosphatemia may develop. *Fleet Enema* has a high amount of phosphorus that can be absorbed, especially in the patient with an ileus. Infants and children with Hirschsprung disease are especially vulnerable. There is often associated hypernatremia owing to sodium absorption and water loss from diarrhea. Sodium phosphorus laxatives may cause hyperphosphatemia if the dose is excessive or if renal insufficiency is present. Hyperphosphatemia occurs in children who receive overly aggressive treatment for hypophosphatemia. Vitamin D intoxication causes excessive gastrointestinal absorption of both calcium and phosphorus, and the suppression of PTH by hypercalcemia decreases renal phosphorus excretion.

The absence of PTH in *pseudohypoparathyroidism* or PTH responsiveness in *pseudohypoparathyroidism* causes hyperphosphatemia because of increased resorption of phosphorus in the proximal tubule of the kidney (see Chapters 571 and 572). The associated hypocalcemia is responsible for the clinical symptoms. The hyperphosphatemia in hyperparathyroidism or acromegaly is usually minor. It is secondary to increased resorption of phosphorus in the proximal tubule from the actions of thyroxine or growth hormone. Excessive thyroxine can also cause bone resorption, which may contribute to the hyperphosphatemia and cause hypercalcemia. Patients with *familial tumoral calcinosis*, a rare autosomal recessive disorder, have hyperphosphatemia as a result of decreased renal phosphate excretion and heterotopic calcifications. The disease may be secondary to mutations in the genes for a glycosyltransferase, the phospha tin FGF-23, or the gene for Klotho, which encodes the coreceptor for FGF-23.

**Clinical Manifestations**

The primary clinical consequences of hyperphosphatemia are hypocalcemia and systemic calcification. The hypocalcemia is probably due to decreased deposition of calcium-phosphorus salt, inhibition of 1,25-dihydroxyvitamin D production, and decreased bone resorption. Symptomatic hypocalcemia is most likely to occur when the phosphorus level increases rapidly or when diseases predisposing to hypocalcemia are present (chronic renal failure, rhabdomyolysis). Systemic calcification occurs because the solubility of phosphorus and calcium in the plasma is exceeded. This is believed to happen when plasma calcium × plasma phosphorus, both measured in mg/dL, is >70. Clinically, this condition is often apparent in the conjunctiva, where it manifests as a foreign-body feeling, erythema, and injection. More ominous manifestations are hypoxia from pulmonary calcification and renal failure from nephrocalcinosis.

**Diagnosis**

Plasma creatinine and BUN levels should be assessed in any patient with hyperphosphatemia. The history should focus on intake of phosphorus and the presence of chronic diseases that may cause hyperphosphatemia. Measurement of potassium, uric acid, calcium, lactate dehydrogenase, bilirubin, hemoglobin, and CPK may be indicated if rhabdomyolysis, tumor lysis, or hemolysis is suspected. With mild hyperphosphatemia and significant hypocalcemia, measurement of the serum PTH level distinguishes between hypoparathyroidism and pseudohypoparathyroidism.

**Treatment**

The treatment of acute hyperphosphatemia depends on its severity and etiology. Mild hyperphosphatemia in a patient with reasonable renal function spontaneously resolves; the resolution can be accelerated by dietary phosphorus restriction. If kidney function is not impaired, then intravenous fluids can enhance renal phosphorus excretion. For more significant hyperphosphatemia or a situation such as tumor lysis or rhabdomyolysis, in which endogenous phosphorus generation is likely to continue, addition of an oral phosphorus binder prevents absorption of dietary phosphorus and can remove phosphorus from the body by binding what is normally secreted and absorbed by the gastrointestinal tract. Phosphorus binders are most effective when given with food.

Binders containing aluminum hydroxide are especially efficient, but calcium carbonate is an effective alternative and may be preferred if there is a need to treat concomitant hypocalcemia. Preservation of renal function, for example with high urine flow in rhabdomyolysis or tumor lysis, is an important adjunct because it will permit continued excretion of phosphorus. If the hyperphosphatemia is not responding to conservative management, especially if renal insufficiency is supervening, then dialysis may be necessary to increase phosphorus removal.

Dietary phosphorus restriction is necessary for diseases causing chronic hyperphosphatemia. However, such diets are often difficult to follow, given the abundance of phosphorus in a variety of foods. Dietary restriction is often sufficient in conditions such as hypoparathyroidism and mild renal insufficiency. For more problematic hyperphosphatemia, such as with moderate renal insufficiency and end-stage renal disease, phosphorus binders are usually necessary. They include calcium carbonate, calcium acetate, sevelamer, and lanthanum. Aluminum-containing phosphorus binders are no longer used in chronic renal insufficiency because of the risk of aluminum toxicity. Dialysis directly removes phosphorus from the blood in patients with end-stage renal disease, but it is only an adjunct to dietary restriction and phosphorus binders, in that elimination of phosphorus by dialysis is not efficient enough to keep up with normal dietary intake.

**Bibliography is available at Expert Consult.**

55.7 Acid–Base Balance

Larry A. Greenbaum

**ACID–BASE PHYSIOLOGY**

**Introduction and Terminology**

Chronic, mild derangements in acid–base status may interfere with normal growth and development, whereas acute, severe changes in pH can be fatal. Control of acid–base balance depends on the kidneys, the lungs, and intracellular and extracellular buffers.

A normal pH is 7.35-7.45. There is an inverse relationship between the pH and the hydrogen ion concentration. At a pH of 7.40, the hydrogen ion concentration is 40 mmol/L. A normal serum sodium concentration, 140 mEq/L, is 1 million times higher. Maintaining a normal pH is necessary because hydrogen ions are highly reactive and are especially likely to combine with proteins, altering their function.

An acid is a substance that releases ("donates") a hydrogen ion (H⁺). A base is a substance that accepts a hydrogen ion. An acid (HA) can dissociate into a hydrogen ion and a conjugate base (A⁻), as follows:

\[
HA \leftrightarrow H^+ + A^- 
\]

A strong acid is highly dissociated, so in this reaction, there is little HA. A weak acid is poorly dissociated; not all of the hydrogen ions are released from HA. A⁻ acts as a base when the reaction moves to the left. These reactions are in equilibrium. When HA is added to the system, there is dissociation of some HA until the concentrations of H⁺ and A⁻ increase enough that a new equilibrium is reached. Addition of hydrogen ions causes a decrease in A⁻ and an increase in HA. Addition of A⁻ causes a decrease in hydrogen ions and an increase in HA.

**Buffers** are substances that attenuate the change in pH that occurs when acids or bases are added to the body. Given the extremely low
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concentration of hydrogen ions in the body at physiologic pH, without buffers a small amount of hydrogen ions could cause a dramatic decline in the pH. Buffers prevent the decrease in pH by binding the added hydrogen ions, as follows:

\[ A^- + H^+ \rightarrow HA \]

The increase in hydrogen ion concentration drives this reaction to the right. Similarly, when base is added to the body, buffers prevent the pH from increasing by releasing hydrogen ions, as follows:

\[ HA \rightarrow A^- + H^+ \]

The best buffers are weak acids and bases. This is because a buffer works best when it is 50% dissociated (half HA and half A⁻). The pH at which a buffer is 50% dissociated is its pK (ionization constant of acid). The best physiologic buffers have a pK close to 7.40. The concentration of a buffer and its pK determine the buffer’s effectiveness (buffering capacity). When the pH is lower than the pK of a buffer, there is more HA than A⁻. When the pH is higher than the pK, there is more A⁻ than HA.

**Physiologic Buffers**

The bicarbonate and nonbicarbonate buffers protect the body against major changes in pH. The bicarbonate buffer system is routinely monitored clinically. The bicarbonate buffer system is based on the relationship between carbon dioxide (CO₂) and bicarbonate (HCO₃⁻):

\[ \text{CO}_2 + \text{H}_2\text{O} \rightarrow \text{H}^+ + \text{HCO}_3^- \]

Carbon dioxide acts as an acid in that, after combining with water, it releases a hydrogen ion: bicarbonate acts as its conjugate base in that it accepts a hydrogen ion. The pK of this reaction is 6.1. The Henderson-Hasselbalch equation expresses the relationship among pH, pK, and the concentrations of an acid and its conjugate base. This relationship is valid for any buffer. The Henderson-Hasselbalch equation for bicarbonate and carbon dioxide is as follows:

\[ \text{pH} = 6.1 + \log[\text{HCO}_3^-]/[\text{CO}_2] \]

The Henderson-Hasselbalch equation for the bicarbonate buffer system has 3 variables: pH, [HCO₃⁻], and [CO₂]. Thus, if any 2 of these variables are known, it is possible to calculate the third. When one is using the Henderson-Hasselbalch equation, it is important that carbon dioxide and bicarbonate have the same units. Carbon dioxide is reported clinically as mm Hg and must be multiplied by its solubility constant, 0.03 mmol/L/mm Hg, before the Henderson-Hasselbalch equation can be used. Mathematical manipulation of the Henderson-Hasselbalch equation produces the following relationship:

\[ [\text{H}^+] = 24 \times \text{PCO}_2/[\text{HCO}_3^-] \]

At a normal hydrogen ion concentration of 40 nmol (pH 7.40), the partial pressure of carbon dioxide (PCO₂), which is expressed as mm Hg in this equation, is 40 when the bicarbonate concentration is 24 mEq/L. This equation emphasizes that the hydrogen ion concentration, and hence pH, can be determined by the ratio of PCO₂ and the bicarbonate concentration.

The bicarbonate buffer system is very effective as a result of the high concentration of bicarbonate in the body (24 mEq/L) and the fact that it is an open system. The remaining body buffers are in a closed system. The bicarbonate buffer system is an open system because the lungs increase carbon dioxide excretion when the blood carbon dioxide concentration increases. When acid is added to the body, the following reaction occurs:

\[ \text{H}^+ + \text{HCO}_3^- \rightarrow \text{CO}_2 + \text{H}_2\text{O} \]

In a closed system, the CO₂ would increase. The higher CO₂ concentration would lead to an increase in the reverse reaction:

\[ \text{CO}_2 + \text{H}_2\text{O} \rightarrow \text{H}^+ + \text{HCO}_3^- \]

This would increase the concentration of hydrogen ions, limiting the buffering capacity of bicarbonate. However, because the lungs excrete the excess carbon dioxide, the reverse reaction does not increase; this fact enhances the buffering capacity of bicarbonate. The same principle holds with the addition of base, because the lungs decrease carbon dioxide excretion and prevent the level of carbon dioxide from falling. The lack of change in carbon dioxide concentration dramatically increases the buffering capacity of bicarbonate.

The nonbicarbonate buffers include proteins, phosphate, and bone. Protein buffers consist of extracellular proteins, mostly albumin and intracellular proteins, including hemoglobin. Proteins are effective buffers, largely because of the presence of the amino acid histidine, which has a side chain that can bind or release hydrogen ions. The pK of histidine varies slightly, depending on its position in the protein molecule, but its average pK is approximately 6.5. This is close enough to a normal pH (7.4) to make histidine an effective buffer. Hemoglobin and albumin have 34 and 16 histidine molecules, respectively.

Phosphate can bind up to 3 hydrogen molecules, so it can exist as PO₄³⁻, HPO₄²⁻, H₂PO₄⁻, or H₃PO₄. However, at a physiologic pH, most phosphate exists as either HPO₄²⁻ or H₂PO₄⁻. H₂PO₄⁻ is an acid, and HPO₄²⁻ is its conjugate base:

\[ \text{H}_2\text{PO}_4^- \leftrightarrow \text{H}^+ + \text{HPO}_4^{2-} \]

The pK of this reaction is 6.8, making phosphate an effective buffer. The concentration of phosphate in the extracellular space is relatively low, limiting the overall buffering capacity of phosphate; it is less important than albumin. However, phosphate is found at a much higher concentration in the urine, where it is an important buffer. In the intracellular space, most phosphate is covalently bound to organic molecules (ATP), but it still serves as an effective buffer.

Bone is an important buffer. Bone is basic—it is composed of compounds such as sodium bicarbonate and calcium carbonate—and thus, dissolution of bone releases base. This release can buffer an acid load, although at the expense of bone density, if it occurs over an extended period. In contrast, bone formation, by consuming base, helps buffer excess base.

Clinically, we measure the extracellular pH, but it is the intracellular pH that affects cell function. Measurement of the intracellular pH is unnecessary because changes in the intracellular pH parallel the changes in the extracellular pH. However, the change in the intracellular pH tends to be less than the change in the extracellular pH because of the greater buffering capacity in the intracellular space.

**NORMAL ACID–BASE BALANCE**

The lungs and kidneys maintain a normal acid–base balance. Carbon dioxide generated during normal metabolism is a weak acid. The lungs prevent an increase in the PCO₂ in the blood by excreting the CO₂ that the body produces. CO₂ production varies according to the body’s metabolic needs, increasing with physical activity. The rapid pulmonary response to changes in the CO₂ concentration occurs via central sensing of the PCO₂ and a subsequent increase or decrease in ventilation to maintain a normal PCO₂ (35-45 mm Hg). An increase in ventilation decreases the PCO₂, and a decrease in ventilation increases the PCO₂.

The kidneys excrete endogenous acid. An adult normally produces approximately 1-2 mEq/kg/24 hr of hydrogen ions. Children normally produce 2-3 mEq/kg/24 hr of hydrogen ions. The 3 principal sources of hydrogen ions are dietary protein metabolism, incomplete metabolism of carbohydrates and fat, and stool losses of bicarbonate. Because metabolism of protein generates hydrogen ions, endogenous acid production varies with protein intake. The complete oxidation of carbohydrates or fats to carbon dioxide and water does not generate hydrogen ions; the lungs remove the carbon dioxide. However, incomplete metabolism of carbohydrates or fats produces hydrogen ions. Incomplete glucose metabolism can produce lactic acid, and incomplete triglyceride metabolism can produce ketoc acids, such as β-hydroxybutyric acid and acetoacetic acid. There is always some baseline incomplete metabolism that contributes to endogenous acid production. This factor increases in pathologic conditions, such as lactic acidosis and diabetic ketoacidosis. Stool loss of bicarbonate is the third major source of endogenous acid production. The stomach secretes hydrogen ions,
but most of the remainder of the gastrointestinal tract secretes bicarbonate, and the net effect is a loss of bicarbonate from the body. To secrete bicarbonate, the cells of the intestine produce hydrogen ions that are released into the bloodstream. For each bicarbonate molecule lost in the stool, the body gains 1 hydrogen ion. This source of endogenous acid production is normally minimal but may increase dramatically in a patient with diarrhea.

The hydrogen ions formed from endogenous acid production are neutralized by bicarbonate, potentially causing the bicarbonate concentration to decrease. The kidneys regenerate this bicarbonate by secreting hydrogen ions. The lungs cannot regenerate bicarbonate, even though loss of carbon dioxide lowers the hydrogen ion concentration, as shown in the following reaction:

\[ \text{H}^+ + \text{HCO}_3^- \rightarrow \text{CO}_2 + \text{H}_2\text{O} \]

A decrease in CO₂ concentration causes the reaction to move to the right, which decreases the hydrogen ion concentration, but it also lowers the bicarbonate concentration. During a metabolic acidosis, hyperventilation can lower the CO₂ concentration, decrease the hydrogen ion concentration, and thus increase the pH. The underlying metabolic acidosis is still present. Similarly, the kidneys cannot correct an abnormally high CO₂ concentration, as shown in the following reaction:

\[ \text{H}^+ + \text{HCO}_3^- \rightarrow \text{CO}_2 + \text{H}_2\text{O} \]

An increase in the bicarbonate concentration also causes the reaction to move to the right, which increases the CO₂ concentration while simultaneously decreasing the hydrogen ion concentration. During a respiratory acidosis, increased renal generation of bicarbonate can decrease the hydrogen ion concentration and increase the pH, but cannot repair the respiratory acidosis. Both the lungs and the kidneys can affect the hydrogen ion concentration and hence the pH. However, only the lungs can regulate the CO₂ concentration, and only the kidneys can regulate the bicarbonate concentration.

**Renal Mechanisms**

The kidneys regulate the serum bicarbonate concentration by modifying acid excretion in the urine. This requires a 2-step process. First, the renal tubules resorb the bicarbonate that is filtered at the glomerulus. Second, there is tubular secretion of hydrogen ions. The urinary excretion of hydrogen ions generates bicarbonate that neutralizes endogenous acid production. The tubular actions necessary for renal acid excretion occur throughout the nephron (Fig. 55-6).

The resorption of filtered bicarbonate is a necessary first step in renal regulation of the acid–base balance. A normal adult has a GFR of approximately 180 L/24 hr. This fluid enters the Bowman space with a bicarbonate concentration that is essentially identical to the plasma concentration, normally 24 mEq/L. Multiplying 180 L by 24 mEq/L indicates that >4,000 mEq of bicarbonate enters the Bowman space each day. This bicarbonate, if not reclaimed along the nephron, would be lost in the urine and would cause a profound metabolic acidosis.

The proximal tubule reclaims approximately 85% of the filtered bicarbonate (Fig. 55-7). The final 15% is reclaimed beyond the proximal tubule, mostly in the ascending limb of the loop of Henle. Bicarbonate molecules are not transported from the tubular fluid into the cells of the proximal tubule. Rather, hydrogen ions are secreted into the tubular fluid, leading to conversion of filtered bicarbonate into CO₂ and water. The secretion of hydrogen ions by the cells of the proximal tubule is coupled to generation of intracellular bicarbonate, which is transported across the basolateral membrane of the proximal tubule cell and enters the capillaries. The bicarbonate produced in the cell replaces the bicarbonate filtered at the glomerulus.

Increased bicarbonate resorption by the cells of the proximal tubule—the result of increased hydrogen ion secretion—occurs in a variety of clinical situations. Volume depletion increases bicarbonate resorption. This is partially mediated by activation of the renin–angiotensin system; angiotensin II increases bicarbonate resorption. Increased bicarbonate resorption in the proximal tubule is one of the mechanisms that accounts for the metabolic alkalosis that may occur in some patients with volume depletion. Other stimulants that increase bicarbonate resorption include hypokalemia and an increased PCO₂. This partially explains the observations that hypokalemia causes a metabolic alkalosis and that a respiratory acidosis leads to a compensatory increase in serum bicarbonate concentration.

Stimuli that decrease bicarbonate resorption in the proximal tubule may cause a decrease in the serum bicarbonate concentration. A decrease in the PCO₂ (respiratory alkalosis) decreases proximal tubule bicarbonate resorption, partially mediating the decrease in serum bicarbonate concentration that compensates for a respiratory alkalosis.

![Figure 55-7 Resorption of filtered bicarbonate in the proximal tubule.](image-url)
PTH decreases proximal tubule bicarbonate resorption; hyperparathyroidism may cause a mild metabolic acidosis. A variety of medications and diseases cause a metabolic acidosis by impairing bicarbonate resorption in the proximal tubule. Examples are the medication acetazolamide, which directly inhibits carbonic anhydrase, and the many disorders that cause proximal RTA (see Chapter 329).

After reclaiming filtered bicarbonate, the kidneys perform the second step in renal acid-base handling, the excretion of the acid created by endogenous acid production. Excretion of acid occurs mostly in the collecting duct, with a small role for the distal tubule.

Along with secretion of hydrogen ions by the tubular cells lining the collecting duct, adequate excretion of endogenous acid requires the presence of urinary buffers. The hydrogen pumps in the collecting duct cannot lower the urine pH below 4.5. The hydrogen ion concentration at pH 4.5 is <0.04 mEq/L; it would require >25 L of water with a pH of 4.5 to excrete 1 mEq of hydrogen ions. A 10-kg child, with an endogenous acid production of 20 mEq of hydrogen ions each day, would need to have a daily urinary output of >500 L without the presence of urinary buffers. As in the blood, buffers in the urine attenuate the decrease in pH that occurs with the addition of hydrogen ions. The 2 principal urinary buffers are phosphate and ammonia.

Urinary phosphate is proportional to dietary intake. Whereas most of the phosphate filtered at the glomerulus is resorbed in the proximal tubule, the urinary phosphate concentration is usually much greater than the serum phosphate concentration. This arrangement allows phosphate to serve as an effective buffer via the following reaction:

\[ \text{H}^+ + \text{HPO}_4^{2-} \rightarrow \text{H}_2\text{PO}_4^- \]

The pK of this reaction is 6.8, making phosphate an effective buffer as the urinary pH decreases from 7.0 to 5.0 within the collecting duct. Although phosphate is an effective buffer, its buffering capacity is limited by its concentration; there is no mechanism for increasing urinary phosphate excretion in response to changes in acid–base status.

In contrast, ammonia production can be modified, allowing for regulation of acid excretion. The buffering capacity of ammonia is based on the reaction of ammonia with hydrogen ions to form ammonium:

\[ \text{NH}_3 + \text{H}^+ \rightarrow \text{NH}_4^+ \]

The cells of the proximal tubule are the source of the excreted ammonia, mostly through metabolism of glutamine via the following reactions:

\[ \text{Glutamine} \rightarrow \text{NH}_4^+ + \text{glutamate} \]
\[ \text{Glutamine}^- \rightarrow \text{NH}_4^+ + \alpha\text{-ketoglutarate} \]

The metabolism of glutamine generates 2 ammonium ions. In addition, the metabolism of α-ketoglutarate generates 2 bicarbonate molecules. The ammonium ions are secreted into the lumen of the proximal tubule, whereas the bicarbonate molecules exit the proximal tubule cells via the basolateral Na\textsuperscript{+}3HCO\textsubscript{3}\textsuperscript{−}/cotransporter (see Fig. 55-6). This arrangement would seem to accomplish the goal of excreting hydrogen ions (as NH\textsubscript{4}\textsuperscript{+}) and regenerating bicarbonate molecules. However, the ammonium ions secreted in the proximal tubule do not remain within the tubular lumen. Cells of the TAL of the loop of Henle resorb the ammonium ions. The result is that there is a high medullary interstitial concentration of ammonia, but the tubular fluid entering the collecting duct does not have significant amounts of ammonium ions. Moreover, the hydrogen ions that were secreted with ammonia, as ammonium ions, in the proximal tubule enter the bloodstream, canceling the effect of the bicarbonate generated in the proximal tubule. The excretion of ammonium ions, and hence of hydrogen ions, depends on the cells of the collecting duct.

The cells of the collecting duct secrete hydrogen ions and regenerate bicarbonate, which is returned to the bloodstream (Fig. 55-8). This bicarbonate neutralizes endogenous acid production. Phosphate and ammonia buffer the hydrogen ions secreted by the collecting duct. Ammonia is an effective buffer because of the high concentrations in the medullary interstitium and because the cells of the collecting duct are permeable to ammonia but not to ammonium. As ammonia diffuses into the lumen of the collecting duct, the low urine pH causes almost all of the ammonia to be converted into ammonium. This process maintains a low luminal ammonia concentration. Because the luminal pH is lower than the pH in the medullary interstitium, there is a higher concentration of ammonia within the medullary interstitium than in the tubular lumen, favoring movement of ammonia into the tubular lumen. Even though the concentration of ammonium in the tubular lumen is higher than in the interstitium, the cells of the collecting duct are impermeable to ammonium, preventing back-diffusion of ammonium out of the tubular lumen and permitting ammonia to be an effective buffer. The kidneys adjust hydrogen ion excretion according to physiologic needs. There is variation in endogenous acid production, largely a result of diet and pathophysiologic stresses, such as diarrheal losses of bicarbonate, which increase the need for acid excretion. Hydrogen excretion is increased by upregulation of hydrogen ion secretion in the collecting duct, causing the pH of the urine to decrease. This response is fairly prompt, occurring within hours of an acid load, but it is limited by the buffering capacity of the urine; the hydrogen pumps in the collecting duct cannot lower the pH to <4.5. A more significant increase in acid excretion requires upregulation of ammonia production by the proximal tubule so that more ammonia is available to serve as a buffer in the tubular lumen of the collecting duct. This response to a low serum pH reaches its maximum within 5-6 days; ammonia excretion can increase approximately 10-fold over the baseline value.

Acid excretion by the collecting duct increases in a number of different clinical situations. The extracellular pH is the most important regulator of renal acid excretion. A decrease in the extracellular pH from either a respiratory or a metabolic acidosis causes an increase in renal acid excretion. Aldosterone stimulates hydrogen ion excretion in the collecting duct, causing an increase in the serum bicarbonate concentration. This explains the metabolic alkalosis that occurs with primary hyperaldosteronism or secondary hyperaldosteronism caused by volume depletion. Hypokalemia increases acid secretion, by both stimulating ammonia production in the proximal tubule and increasing hydrogen ion secretion in the collecting duct. Hypokalemia therefore tends to produce a metabolic alkalosis. Hyperkalemia has the opposite effects, which may cause a metabolic acidosis.

In patients with an increased pH, the kidney has 2 principal mechanisms for correcting the problem. First, less bicarbonate is resorbed in the proximal tubule, leading to an increase in urinary bicarbonate...
losses. Second, in a limited number of specialized cells, the process for secretion of hydrogen ions by the collecting duct (see Fig. 55-8) can be reversed, leading to secretion of bicarbonate into the tubular lumen and secretion of hydrogen ions into the peritubular fluid, where they enter the bloodstream.

**CLINICAL ASSESSMENT OF ACID–BASE DISORDERS**

The following equation, a rearrangement of the Henderson–Hasselbalch equation, emphasizes the relationship among the PCO₂, the bicarbonate concentration, and the hydrogen ion concentration:

\[
[H^+] = 24 \times \frac{PCO_2}{[HCO_3^-]}
\]

An increase in the PCO₂ or a decrease in the bicarbonate concentration increases the hydrogen ion concentration; the pH decreases. A decrease in the PCO₂ or an increase in the bicarbonate concentration decreases the hydrogen ion concentration; the pH increases.

**Terminology**

Acidemia is a pH below normal (<7.35), and alkalemia is a pH above normal (>7.45). An acidosis is a pathologic process that causes an increase in the hydrogen ion concentration, and an alkalosis is a pathologic process that causes a decrease in the hydrogen ion concentration. Whereas acidemia is always accompanied by an acidosis, a patient can have an acidosis and a low, normal, or high pH. For example, a patient may have a mild metabolic acidosis but a simultaneous, severe respiratory alkalosis; the net result may be alkalemia. Acidemia and alkalemia indicate the pH abnormality; acidosis and alkalosis indicate the pathologic process that is taking place.

A simple acid–base disorder is a single primary disturbance. During a simple metabolic disorder, there is respiratory compensation. With a metabolic acidosis, the decrease in the pH increases the ventilatory drive, causing a decrease in the PCO₂. The decrease in the CO₂ concentration leads to an increase in the pH. This appropriate respiratory compensation is expected with a primary metabolic acidosis. Despite the decrease in the CO₂ concentration, appropriate respiratory compensation is not a respiratory alkalosis, even though it is sometimes erroneously called a compensatory respiratory alkalosis. A low PCO₂ can be either the result of a primary respiratory alkalosis or of an appropriate respiratory compensation for a metabolic acidosis. Appropriate respiratory compensation also occurs with a primary metabolic alkalosis, although in this case the CO₂ concentration increases to attenuate the increase in the pH. The respiratory compensation for a metabolic process happens quickly and is complete within 12-24 hr; it cannot overcompensate for or normalize the pH.

During a primary respiratory process, there is metabolic compensation, mediated by the kidneys. The kidneys respond to a respiratory acidosis by increasing hydrogen ion excretion, thereby increasing bicarbonate generation and raising the serum bicarbonate concentration. The kidneys increase bicarbonate excretion to compensate for a respiratory alkalosis; the serum bicarbonate concentration decreases. Unlike respiratory compensation, which occurs rapidly, it takes 3-4 days for the kidneys to complete appropriate metabolic compensation. There is, however, a small and rapid compensatory change in the bicarbonate concentration during a primary respiratory process. The expected appropriate metabolic compensation for a respiratory disorder depends on whether the process is acute or chronic.

A mixed acid–base disorder is present when there is more than 1 primary acid–base disturbance. An infant with bronchopulmonary dysplasia may have a respiratory acidosis from chronic lung disease and a metabolic alkalosis from the furosemide used to treat the chronic lung disease. More dramatically, a child with pneumonia and sepsis may have severe acidemia as a result of a combined metabolic acidosis caused by lactic acid and respiratory acidosis caused by ventilatory failure.

There are formulas for calculating the appropriate metabolic or respiratory compensation for the 6 primary simple acid–base disorders (Table 55-11). The appropriate compensation is expected in a simple disorder; it is not optional. If a patient does not have the appropriate compensation, then a mixed acid–base disorder is present. A patient has a primary metabolic acidosis with a serum bicarbonate concentration of 10 mEq/L. The expected respiratory compensation is a CO₂ concentration of 23 mm Hg ± 1 (1.5 × 10 + 8 ± 2 = 23 ± 2; Table 55-11). If the patient's CO₂ concentration is >25 mm Hg, a concurrent respiratory acidosis is present; the CO₂ concentration is higher than expected. A patient may have a respiratory acidosis despite a CO₂ level below the “normal” value of 35-45 mm Hg. In this example, a CO₂ concentration <21 mm Hg indicates a concurrent respiratory alkalosis; the CO₂ concentration is lower than expected.

**Diagnosis**

A systematic evaluation of an arterial blood gas sample, combined with the clinical history, can usually explain the patient's acid–base disturbance. Assessment of an arterial blood gas sample requires knowledge of normal values (Table 55-12). In most cases, this is accomplished via a 3-step process (Fig. 55-9):

- Determine whether acidemia or alkalemia is present.
- Determine whether acidemia or alkalemia is present.
- Determine whether a mixed disorder is present.

Most patients with an acid–base disturbance have an abnormal pH, although there are 2 exceptions. The first exception is in the patient with a mixed disorder, wherein the 2 processes have opposite effects on pH (a metabolic acidosis and a respiratory alkalosis) and cause changes in the hydrogen ion concentration that are comparable in magnitude, albeit opposite. The second exception is in the patient with a simple chronic respiratory alkalosis; in some instances, the appropriate metabolic compensation is enough to normalize the pH. In both of these situations, the presence of an acid–base disturbance is deduced because of the abnormal CO₂ and/or bicarbonate levels. Determining the acid–base disturbance in these situations requires proceeding to the third step of this process.

The second step requires inspection of the serum bicarbonate and CO₂ concentrations to determine a cause of the abnormal pH (see Fig. 55-9). In most cases, there is only 1 obvious explanation for the abnormal pH. In some mixed disorders, however, there may be 2 possibilities (a high PCO₂ and a low [HCO₃⁻] in a patient with acidemia). In such cases, the patient has 2 causes for abnormal pH (a metabolic acidosis and a respiratory acidosis, in this instance), and it is unnecessary to proceed to the third step.

The third step requires determining whether the patient's compensation is appropriate. It is assumed that the primary disorder
was diagnosed in the second step, and the expected compensation is calculated (see Table 55-11). If the compensation is appropriate, then a simple acid–base disorder is present. If the compensation is not appropriate, then a mixed disorder is present. The identity of the second disorder is determined by deciding whether the compensation is too little or too much compared with what was expected (see Fig. 55-9).

The history is always useful in evaluating and diagnosing patients with acid–base disturbances. It is especially helpful in a respiratory process. The expected metabolic compensation for a respiratory process changes according to whether the process is acute or chronic, which can be deduced only from the history. The metabolic compensation for an acute respiratory acidosis is less than that for a chronic respiratory acidosis. In a patient with a respiratory acidosis, a small increase in the bicarbonate concentration would be consistent with a simple acute respiratory acidosis or a mixed disorder (a chronic respiratory acidosis and a metabolic acidosis). Only the history can differentiate among the possibilities. Knowledge of the length of the respiratory process and the presence or absence of a risk factor for a metabolic acidosis (diarrhea) allows the correct conclusion to be reached.

**METABOLIC ACIDOSIS**

Metabolic acidosis occurs frequently in hospitalized children; diarrhea is the most common etiology. For a patient with an unknown medical problem, the presence of a metabolic acidosis is often helpful diagnostically, because it suggests a relatively narrow differential diagnosis.

Patients with a metabolic acidosis have a low serum bicarbonate concentration, although not every patient with a low serum bicarbonate concentration has a metabolic acidosis. The exception is the patient with a respiratory alkalosis, which causes a decrease in the serum bicarbonate concentration as part of appropriate renal compensation. In a patient with an isolated metabolic acidosis, there is a predictable decrease in the blood CO2 concentration, as follows:

\[
\text{PCO}_2 = 1.5 \times [\text{HCO}_3^-] + 8 \pm 2
\]

A mixed acid–base disturbance is present if the respiratory compensation is not appropriate. If the PCO2 is greater than predicted, then the patient has a concurrent respiratory acidosis. A lower PCO2 than predicted indicates a concurrent respiratory alkalosis or, less commonly, an isolated respiratory alkalosis. Because the appropriate respiratory compensation for a metabolic acidosis never normalizes the patient's pH, the presence of a normal pH and a low bicarbonate concentration occurs only if some degree of respiratory alkalosis is present. In this situation, distinguishing an isolated chronic respiratory alkalosis from a mixed metabolic acidosis and acute respiratory alkalosis may be possible only clinically. In contrast, the combination of a low serum pH and a low bicarbonate concentration occurs only if a metabolic acidosis is present.

**Etiology and Pathophysiology**

There are many causes of a metabolic acidosis (Table 55-13), which occur via 3 basic mechanisms:

- **Loss of bicarbonate from the body**
- **Impaired ability to excrete acid by the kidney**
- **Addition of acid to the body (exogenous or endogenous)**

**Diarrhea**, the most common cause of metabolic acidosis in children, causes a loss of bicarbonate from the body. The amount of bicarbonate lost in the stool depends on the volume of diarrhea and the bicarbonate concentration of the stool, which tends to increase with more severe diarrhea. The kidneys attempt to balance the losses by increasing acid secretion, but metabolic acidosis occurs when this compensation is inadequate. Diarrhea often causes volume depletion as a result of losses of sodium and water, potentially exacerbating the acidosis by causing shock and a lactic acidosis. In addition, diarrhoeal losses of potassium lead to hypokalemia. Moreover, the volume depletion causes increased production of aldosterone. This increase stimulates renal retention of sodium, helping to maintain intravascular volume, but also leads to increased urinary losses of potassium, exacerbating the hypokalemia.

There are 3 forms of RTA: distal (type I), proximal (type II), and hyperkalemic (type IV) (see Chapter 529). In distal RTA, children may have accompanying hypokalemia, hypercalcemia, nephrolithiasis, and nephrocalcinosis. Failure to thrive because of chronic metabolic acidosis is the most common presenting complaint. Patients with distal RTA cannot acidify their urine and, thus, have a urine pH >5.5 despite a metabolic acidosis.

Proximal RTA is rarely present in isolation. In most patients, proximal RTA is part of Fanconi syndrome, a generalized dysfunction of the proximal tubule. The dysfunction leads to glycosuria, aminoaciduria, and excessive urinary losses of phosphate and uric acid. The presence of a low serum uric acid level, glycosuria, and aminoaciduria is helpful diagnostically. Chronic hypophosphatemia leads to rickets in children (see Chapter 51). Rickets and/or failure to thrive may be the presenting complaint. The ability to acidify the urine is intact in proximal RTA; thus, untreated patients have a urine pH <5.5. However, bicarbonate therapy increases bicarbonate losses in the urine, and the urine pH increases.

In hyperkalemic RTA, renal excretion of acid and potassium is impaired. Hyperkalemic RTA is the result of either an absence of

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**Figure 55-9** Three-step process for interpreting acid–base disturbances. In step 1, determine whether the pH is low (acidemia) or high (alkalemia). In step 2, establish an explanation for the acidemia or alkalemia. In step 3, calculate the expected compensation (see Table 55-11) and determine whether a mixed disturbance is present. Met. Acid., metabolic acidosis; Met. Alk., metabolic alkalosis; Resp. Acid., respiratory acidosis; Resp. Alk., respiratory alkalosis.
Causes of Metabolic Acidosis

<table>
<thead>
<tr>
<th>Table 55-13 Causes of Metabolic Acidosis</th>
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<tbody>
<tr>
<td><strong>NORMAL ANION GAP</strong></td>
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<tr>
<td>Diarrhea</td>
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<tr>
<td>Renal tubular acidosis (RTA):</td>
</tr>
<tr>
<td>Distal (type I) RTA (OMIM 179800/602722/267300)*</td>
</tr>
<tr>
<td>Proximal (type II) RTA (OMIM 604278)</td>
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<tr>
<td>Hyperkalemic (type IV) RTA (OMIM 201910/264350/177735/145260)</td>
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<tr>
<td>Urinary tract diversions</td>
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<tr>
<td>Posthypocapnia</td>
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<td>Ammonium chloride intake</td>
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<tr>
<td><strong>INCREASED ANION GAP</strong></td>
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<tr>
<td>Lactic acidosis</td>
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<tr>
<td>Tissue hypoxia</td>
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<tr>
<td>Shock</td>
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<td>Hypoxemia</td>
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<tr>
<td>Severe anemia</td>
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<td>Liver failure</td>
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<tr>
<td>Malignancy</td>
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<td>Intestinal bacterial overgrowth</td>
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<td>Inborn errors of metabolism</td>
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<tr>
<td>Medications</td>
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<tr>
<td>Nucleoside reverse transcriptase inhibitors</td>
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<td>Ketoacidosis</td>
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<td>Diabetic ketoacidosis</td>
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<td>Starvation ketoacidosis</td>
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<td>Alcoholic ketoacidosis</td>
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<td>Kidney failure</td>
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<td>Poisoning</td>
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<td>Ethylene glycol</td>
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<td>Methanol</td>
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<tr>
<td>Salicylate</td>
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<tr>
<td>Toluene</td>
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<tr>
<td>Paraldehyde</td>
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</table>

*Along with these genetic disorders, distal RTA may be secondary to renal disease or medications.

† Most cases of proximal RTA are not caused by this primary genetic disorder.

* Hypokalemic RTA can be secondary to a genetic disorder (some of the more common are listed) or other etiologies.


aldosterone or an inability of the kidney to respond to aldosterone. In severe aldosterone deficiency, as occurs with congenital adrenal hyperplasia because of 21α-hydroxylase deficiency, the hyperkalemia and metabolic acidosis are accompanied by hyponatremia and volume depletion from renal salt wasting. Incomplete aldosterone deficiency causes less-severe electrolyte disturbances; children may have isolated hyperkalemic RTA, hyperkalemia without acidosis, or isolated hyponatremia. Patients may have aldosterone deficiency caused by decreased renin production by the kidney; renin normally stimulates aldosterone synthesis. Children with hyporeninemic hypoaldosteronism usually have either isolated hyperkalemia or hyperkalemic RTA. The manifestations of aldosterone resistance depend on the severity of the resistance. In the autosomal recessive form of pseudohypoaldosteronism type I, which is the result of an absence of the sodium channel that normally responds to aldosterone, there is often severe salt wasting and hyponatremia. In contrast, the aldosterone resistance in kidney transplant recipients usually produces either isolated hyperkalemia or hyperkalemic RTA; hyponatremia is unusual. Similarly, the medications that cause hyperkalemic RTA do not cause hyponatremia. Pseudohypoaldosteronism type II, an autosomal recessive disorder also known as Gordon syndrome, is a unique cause of hyperkalemic RTA because the genetic defect causes volume expansion and hypertension.

Children with abnormal urinary tracts, usually secondary to congenital malformations, may require diversion of urine through intestinal segments. Ureterosigmoidostomy, anastomosis of a ureter to the sigmoid colon, almost always produces a metabolic acidosis and hypokalemia. Consequently, ileal conduits are now the more commonly used procedure, although there is still a risk of a metabolic acidosis.

The appropriate metabolic compensation for a chronic respiratory alkalosis is a decrease in renal acid excretion. The resultant decrease in the serum bicarbonate concentration lessens the alkalemia caused by the respiratory alkalosis. If the respiratory alkalosis resolves quickly, the patient continues to have a decreased serum bicarbonate concentration, causing acidemia as the result of a metabolic acidosis. This resolves over 1-2 days via increased acid excretion by the kidneys.

Lactic acidosis most commonly occurs when inadequate oxygen delivery to the tissues leads to anaerobic metabolism and excess production of lactic acid. Lactic acidosis may be secondary to shock, severe anemia, or hypoxemia. When the underlying cause of the lactic acidosis is alleviated, the liver is able to metabolize the accumulated lactate into bicarbonate, correcting the metabolic acidosis. There is normally some tissue production of lactate that is metabolized by the liver. In children with severe liver dysfunction, impairment of lactate metabolism may produce a lactic acidosis. Rarely, a metabolically active malignancy grows so fast that its blood supply becomes inadequate, with resultant anaerobic metabolism and lactic acidosis. Patients who have short bowel syndrome resulting from small bowel resection can have bacterial overgrowth. In these patients, excessive bacterial metabolism of glucose into d-lactic acid can cause a lactic acidosis. Lactic acidosis occurs in a variety of inborn errors of metabolism, especially those affecting mitochondrial oxidation (see Chapter 87.4).

Finally, medications can cause lactic acidosis. Nucleoside reverse transcriptase inhibitors that are used to treat HIV infection inhibit mitochondrial replication; lactic acidosis is a rare complication, although elevated serum lactate concentrations without acidosis are quite common. Metformin, commonly used for treating type 2 diabetes mellitus, is most likely to cause a lactic acidosis in patients with renal insufficiency. High dosages and prolonged use of propofol can cause lactic acidosis. Propylene glycol is a diluent in a variety of oral and intravenous medications; excessive intake causes a lactic acidosis, principally from accumulation of d-lactic acid.

In insulin-dependent diabetes mellitus, inadequate insulin leads to hyperglycemia and diabetic ketoacidosis (see Chapter 589). Production of acetoacetic acid and β-hydroxybutyric acid causes the metabolic acidosis. Administration of insulin corrects the underlying metabolic problem and permits conversion of acetoacetate and β-hydroxybutyrate into bicarbonate, which helps correct the metabolic acidosis. However, in some patients, urinary losses of acetoacetic acid and β-hydroxybutyrate may be substantial, preventing rapid regeneration of bicarbonate. In these patients, full correction of the metabolic acidosis requires renal regeneration of bicarbonate, a slower process. The hyperglycemia causes an osmotic diuresis, usually producing volume depletion, along with substantial losses of potassium, sodium, and phosphate.

In starvation ketoacidosis, the lack of glucose leads to keto acid production, which, in turn, can produce a metabolic acidosis, although it is usually mild as a result of increased acid secretion by the kidney. In alcoholic ketoacidosis, which is much less common in children than in adults, the acidosis usually follows a combination of an alcoholic binge with vomiting and poor intake of food. The acidosis is potentially more severe than with isolated starvation, and the blood glucose level may be low, normal, or high. Hypoglycemia and acidosis also suggest an inborn error of metabolism.

Renal failure causes a metabolic acidosis because of the need for the kidneys to excrete the acid produced by normal metabolism. With mild or moderate renal insufficiency, the remaining nephrons are usually able to compensate by increasing acid excretion. When the GFR is <20-30% of normal, the compensation is inadequate and a metabolic acidosis develops. In some children, especially those with chronic renal failure because of tubular damage, the acidosis develops at a higher GFR because of a concurrent defect in acid secretion by the distal tubule (distal RTA).

A variety of toxic ingestions (see Chapter 63) can cause a metabolic acidosis. Salicylate intoxication is now much less common because aspirin is no longer recommended for fever control in children. Acute
salicylate intoxication occurs after a large overdose. Chronic salicylate intoxication is possible with gradual buildup of the drug. Especially in adults, respiratory alkalosis may be the dominant acid–base disturbance. In children, the metabolic acidosis is usually the more significant finding. Other symptoms of salicylate intoxication are fever, seizures, lethargy, and coma. Hyperventilation may be particularly marked. Tinnitus, vertigo, and hearing impairment are more likely with chronic salicylate intoxication.

**Ethylene glycol**, a component of antifreeze, is converted in the liver to glyoxylic and oxalic acids, causing a severe metabolic acidosis. Excessive oxalate excretion causes calcium oxalate crystals to appear in the urine, and calcium oxalate precipitation in the kidney tubules can cause renal failure. The toxicity of methanol ingestion also depends on liver metabolism; formic acid is the toxic end product that causes the metabolic acidosis and other sequelae, which include damage to the optic nerve and CNS. Symptoms may include nausea, emesis, visual impairment, and altered mental status. Toluene inhalation and paralytic dehydration ingestion are other potential causes of a metabolic acidosis.

Many inborn errors of metabolism cause a metabolic acidosis (see Chapters 84–87). The metabolic acidosis may be the result of excessive production of keto acids, lactic acid, and/or other organic anions. Some patients have accompanying hypoglycemia or hyperammonemia. In most patients, the acidosis occurs episodically, only during acute decompensations, which may be precipitated by ingestion of specific dietary substrates, the stress of a mild illness, or poor compliance with dietary or medical therapy. In a few inborn errors of metabolism, patients have a chronic metabolic acidosis.

**Clinical Manifestations**
The underlying disorder usually produces most of the signs and symptoms in children with a mild or moderate metabolic acidosis. The clinical manifestations of the acidosis are related to the degree of acidemia; patients with appropriate respiratory compensation and less severe acidemia have fewer manifestations than those with a concomitant respiratory acidosis. At a serum pH < 7.2, there may be impaired cardiac contractility and an increased risk of arrhythmias, especially if underlying heart disease or other predisposing electrolyte disorders are present. With acidemia, there may be a decrease in the cardiovascular response to catecholamines, potentially exacerbating hypotension in children with volume depletion or shock. Acidemia causes vasoconstriction of the pulmonary vasculature, which is especially problematic in newborn infants with persistent pulmonary hypertension (see Chapter 101.7).

The normal respiratory response to metabolic acidosis—compensatory hyperventilation—may be subtle with mild metabolic acidosis, but it causes discernible increased respiratory effort with worsening acidemia. The acute metabolic effects of acidemia include insulin resistance, increased protein degradation, and reduced ATP synthesis. Chronic metabolic acidosis causes failure to thrive in children. Acidemia causes potassium to move from the intracellular space to the extracellular space, thereby increasing the serum potassium concentration. Severe acidemia impairs brain metabolism, eventually resulting in lethargy and coma.

**Diagnosis**
The etiology of a metabolic acidosis is often apparent from the history and physical examination. Acutely, diarrhea and shock are common causes of a metabolic acidosis. Shock, which causes a lactic acidosis, is usually apparent on physical examination and can be secondary to dehydration, acute blood loss, sepsis, or heart disease. Failure to thrive suggests a chronic metabolic acidosis, as happens with renal insufficiency or RTA. New onset of polyuria occurs in children with undiagnosed diabetes mellitus and diabetic ketoacidosis. Metabolic acidosis with seizures and/or a depressed sensorium, especially in an infant, warrants consideration of an inborn error of metabolism. Meningitis and sepsis with lactic acidosis are more common explanations for metabolic acidosis with neurologic signs and symptoms. Identification of a toxic ingestion such as of ethylene glycol or methanol is especially important because of the potentially excellent response to specific therapy. A variety of medications can cause a metabolic acidosis; they may be prescribed or accidentally ingested. Hepatomegaly and metabolic acidosis may occur in children with sepsis, congenital or acquired heart disease, hepatic failure, or inborn errors of metabolism.

Basic laboratory tests in a child with a metabolic acidosis should include measurements of BUN, serum creatinine, serum glucose, urinalysis, and serum electrolytes. Elevated BUN and creatinine values are present in renal insufficiency, whereas an elevated BUN:creatinine ratio (>20:1) supports a diagnosis of prerenal azotemia and the possibility of poor perfusion with lactic acids. Metabolic acidosis, hyperglycemia, glycosuria, and ketonuria support a diagnosis of diabetic ketoacidosis. Starvation causes ketosis, but the metabolic acidosis, if present, is usually mild (HCO$_3^-$ > 18). In most children with ketosis from poor intake and metabolic acidosis there is a concomitant disorder, such as gastroenteritis with diarrhea, that explains the metabolic acidosis. Alternatively, metabolic acidosis with or without ketosis occurs in inborn errors of metabolism; patients with these disorders may have hyperglycemia, normoglycemia, or hypoglycemia. Adrenal insufficiency may cause metabolic acidosis and hypoglycemia. Metabolic acidosis with hypoglycemia also occurs with liver failure. Metabolic acidosis, normoglycemia, and glycosuria occur in children when type II RTA is part of Fanconi syndrome; the defect in resorption of glucose by the proximal tubule of the kidney causes the glycosuria.

The serum potassium level is often abnormal in children with a metabolic acidosis. Even though a metabolic acidosis causes potassium to move from the intracellular space to the extracellular space, many patients with a metabolic acidosis have a low serum potassium level owing to excessive body losses of potassium. In diabetes, there are high stool losses of potassium and often secondary renal losses of potassium, whereas in type I or type II RTA, there are increased urinary losses of potassium. In diabetic ketoacidosis, urinary losses of potassium are high, but the shift of potassium out of cells because of a lack of insulin and metabolic acidosis is especially significant. Consequently, the initial serum potassium level can be low, normal, or high, even though total body potassium is almost always decreased. The serum potassium level is usually increased in patients with acidosis due to renal insufficiency; urinary potassium excretion is impaired. The combination of metabolic acidosis, hyperkalemia, and hyponatremia occurs in patients with severe aldosterone deficiency (adenogenital syndrome) or aldosterone resistance. Patients with less severe, type IV RTA often have only hyperkalemia and metabolic acidosis. Very ill children with metabolic acidosis may have an elevated serum potassium value as a result of a combination of renal insufficiency, tissue breakdown, and a shift of potassium from the intracellular space to the extracellular space secondary to the metabolic acidosis.

The plasma anion gap is useful for evaluating patients with a metabolic acidosis. It divides patients into 2 diagnostic groups, those with normal anion gap and those with increased anion gap. The following formula determines the anion gap:

$$\text{Anion gap} = [\text{Na}^+] - [\text{Cl}^-] - [\text{HCO}_3^-]$$

A normal anion gap is 4–11, although there is variation among laboratories. The number of serum anions must equal the number of serum cations to maintain electrical neutrality (Fig. 55-10). The anion gap is the difference between the measured cation (sodium) and the measured anions (chloride + bicarbonate). The anion gap is also the difference between the unmeasured cations (potassium, magnesium, calcium) and the unmeasured anions (albumin, phosphate, urate, sulfate). An increased anion gap occurs when there is an increase in unmeasured anions. With a lactic acidosis, there is endogenous production of lactic acid, which is composed of positively charged hydrogen ions and negatively charged lactate anions. The hydrogen ions are largely buffered by serum bicarbonate, resulting in a decrease in the bicarbonate concentration. The hydrogen ions that are not buffered by bicarbonate cause the serum pH to decrease. The lactate anions remain, causing the increase in the anion gap.

An increase in unmeasured anions, along with hydrogen ion generation, is present in all causes of an increased gap metabolic acidosis (see Table 55-13). In diabetic ketoacidosis, the keto acids β-hydroxybutyrate
and chloride the of concentrations serum chloride concentration. UC, unmeasured cations. Acidosis. In a nongap metabolic acidosis, there is an increase in the bicarbonate concentration. There is thus a mix of an increased gap and a normal gap metabolic acidosis.

The normal gap metabolic acidosis is especially prominent in children with renal failure as a result of tubular damage, as occurs with renal dysplasia or obstructive uropathy, because these patients have a concurrent RTA. The unmeasured anions in toxic ingestions vary: formate in methanol intoxication, glycolate in ethylene glycol intoxication, and lactate and keto acids in salicylate intoxication. In inborn errors of metabolism, the unmeasured anions depend on the specific etiology which includes hypokalemia and hypophosphatemia. Bicarbonate therapy increases the generation of CO₂, which can accumulate in patients with respiratory failure. Because CO₂ readily diffuses into cells, the administration of bicarbonate can lower the intracellular pH, potentially worsening cell function. Base therapy is usually reserved for children with severe acute lactic acidosis and severe diabetic ketoacidosis.

**Oral base therapy** is given to children with chronic metabolic acidosis. Sodium bicarbonate tablets are available for older children. Younger children generally take citrate solutions; the liver generates bicarbonate from citrate. Citrate solutions are available as sodium citrate, potassium citrate, and a 1:1 mix of sodium citrate and potassium citrate. The patient's potassium needs dictate the choice. Children with type I or type II RTA may have hypokalemia and may benefit from potassium supplements, whereas most children with chronic renal failure cannot tolerate additional potassium.

Oral or intravenous base can be used in acute metabolic acidosis; intravenous therapy is generally used when a rapid response is necessary. Sodium bicarbonate may be given as a bolus, usually at a dose of 1 mEq/kg, in an emergency situation. Another approach is to add sodium bicarbonate or sodium acetate to the patient's intravenous fluids, remembering to remove an equal amount of sodium chloride from the solution to avoid giving an excessive sodium load. Careful monitoring is mandatory so that the dose of base can be titrated appropriately. Tris-hydroxymethyl aminomethane (THAM) is an option in patients with a metabolic acidosis and a respiratory acidosis, because it neutralizes acids without releasing CO₂. THAM also diffuses into cells and therefore provides intracellular buffering.

Hemodialysis is another option for correcting a metabolic acidosis, and it is an appropriate choice in patients with renal insufficiency, especially if significant uremia or hyperkalemia is also present. Hemodialysis is advantageous for correcting the metabolic acidosis caused by methanol or ethylene glycol intoxication, because hemodialysis removes the offending toxin. In addition, these patients often have a severe metabolic acidosis that does not respond easily to intravenous bicarbonate therapy. Peritoneal dialysis is another option for correcting the metabolic acidosis due to renal insufficiency, although, because it relies on lactate as the source of base, it may not correct the metabolic acidosis in patients with concomitant renal failure and lactic acidosis.

**Chapter 55 ♦ Electrolyte and Acid-Base Disorders**

**Figure 55-10** The anion gap, which is the difference between the sodium concentration and the combined concentrations of chloride and bicarbonate (vertical lines). In both a gap and a nongap metabolic acidosis, there is a decrease in the bicarbonate concentration. There is an increase in unmeasured anions (UA) in patients with a gap metabolic acidosis. In a nongap metabolic acidosis, there is an increase in the serum chloride concentration. UC, unmeasured cations.

**Table 55-7** The diagnostic utility of the anion gap. The anion gap is more precise than using the chloride concentration, making the chloride concentration a less reliable predictor of unmeasured anions than the more direct measure, calculation of the anion gap. Conversely, a decrease in unmeasured cations is a very unusual cause of an increased anion gap.

- **Normal anion gap** metabolic acidosis occurs when there is a decrease in the bicarbonate concentration without an increase in the unmeasured anions. With diarrhea, there is a loss of bicarbonate in the stool, causing a decrease in the serum pH and bicarbonate concentration; the serum chloride concentration increases to maintain electrical neutrality (see Fig. 55-10). Hyperchloremic metabolic acidosis is an alternative term for a normal anion gap metabolic acidosis. Calculation of the anion gap is more precise than using the chloride concentration to differentiate between a normal and an increased gap metabolic acidosis, in that the anion gap directly determines the presence of unmeasured anions. Electrical neutrality dictates that the chloride concentration increases or decreases according to the serum sodium concentration, making the chloride concentration a less reliable predictor of unmeasured anions than the more direct measure, calculation of the anion gap.

- **Approximately 11 mEq** of the anion gap is normally secondary to albumin. A 1 g/dL decrease in the albumin concentration decreases the anion gap by roughly 2.5 mEq/L. Similarly, an increase in unmeasured cations, such as calcium, potassium, and magnesium, decreases the anion gap. Conversely, a decrease in unmeasured cations is a very unusual cause of an increased anion gap. Because of these variables, the broad range of a normal anion gap, and other variables, the presence of a normal or an increased anion gap is not always reliable in differentiating among the causes of a metabolic acidosis, especially when the metabolic acidosis is mild. In some patients there is more than 1 explanation for the metabolic acidosis, such as the child with diarrhea and lactic acidosis as a result of poor perfusion. The anion gap should not be interpreted in dogmatic isolation; consideration of other laboratory abnormalities and the clinical history improves its diagnostic utility.

**Treatment**

The most effective therapeutic approach for patients with a metabolic acidosis is repair of the underlying disorder, if possible. The administration of insulin in diabetic ketoacidosis and the restoration of adequate perfusion with intravenous fluids in lactic acidosis because of hypovolemia or shock eventually result in normalization of the acid–base balance. In other diseases, the use of bicarbonate therapy is indicated because the underlying disorder is irreparable. Children with metabolic acidosis caused by RTA or chronic renal failure require long-term base therapy. Patients with acute renal failure and metabolic acidosis need base therapy until their kidneys’ ability to excrete hydrogen normalizes. In other disorders, the cause of the metabolic acidosis eventually resolves, but base therapy is necessary during the acute illness. In salicylate poisoning, alkali administration increases renal clearance of salicylate and decreases the amount of salicylate in brain cells. Short-term base therapy is often necessary in other poisonings (ethylene glycol, methanol) and inborn errors of metabolism (pyruvate carboxylase deficiency, propionic acidemia). Some inborn errors of metabolism require long-term base therapy.

The use of base therapy in diabetic ketoacidosis and lactic acidosis is controversial; there is little evidence that it improves patient outcome, and it has a variety of potential side effects. The risks of giving sodium bicarbonate include the possibility of causing hypernatremia or volume overload. Furthermore, the patient may have overcorrection of the metabolic acidosis once the underlying disorder resolves, because metabolism of lactate or keto acids generates bicarbonate. The rapid change from acidemia to alkalemia can cause a variety of problems, including hypokalemia and hypophosphatemia. Bicarbonate therapy increases the generation of CO₂, which can accumulate in patients with respiratory failure. Because CO₂ readily diffuses into cells, the administration of bicarbonate can lower the intracellular pH, potentially worsening cell function. Base therapy is usually reserved for children with severe acute lactic acidosis and severe diabetic ketoacidosis.
Many causes of metabolic acidosis require specific therapy. Administration of a glucocorticoid and a mineralocorticoid is necessary in patients with adrenal insufficiency. Patients with diabetic ketoacidosis require insulin therapy, whereas patients with lactic acidosis respond to measures that alleviate tissue hypoxia. Along with correction of acidosis, patients with methanol or ethylene glycol ingestion should receive an agent that prevents the breakdown of the toxic substance to its toxic metabolites. Fomepizole has supplanted ethanol as the treatment of choice. These agents work by inhibiting alcohol dehydrogenase, the enzyme that performs the first step in the metabolism of ethylene glycol or methanol. There are a variety of disease-specific therapies for patients with a metabolic acidosis resulting from an inborn error of metabolism.

**METABOLIC ALKALOSIS**

Metabolic alkalosis in children is most commonly secondary to emesis or diuretic use. The serum bicarbonate concentration is increased with a metabolic alkalosis, although a respiratory acidosis also leads to a compensatory elevation of the serum bicarbonate concentration. With a simple metabolic alkalosis, however, the pH is elevated; alkalemia is present. Patients with a respiratory acidosis are acidemic. A metabolic alkalosis, by decreasing ventilation, causes appropriate respiratory compensation. PCO2 decreases by 7 mm Hg for each 10 mEq/L increase in the serum bicarbonate concentration. Appropriate respiratory compensation never exceeds a PCO2 of 55-60 mm Hg. The patient has a concurrent respiratory alkalosis if the PCO2 is lower than the expected compensation. A greater-than-expected PCO2 occurs with a concurrent respiratory acidosis.

**Etiology and Pathophysiology**

The kidneys normally respond promptly to a metabolic alkalosis by increasing base excretion. Two processes are therefore usually present to produce a metabolic alkalosis. The first process is the generation of the metabolic alkalosis, which requires the addition of base to the body. The second process is the maintenance of the metabolic alkalosis, which requires impairment in the kidney’s ability to excrete base.

The etiologies of a metabolic alkalosis are divided into 2 categories on the basis of urinary chloride level (Table 55-14). The alkalosis in patients with a low urinary chloride level is maintained by volume depletion; thus, volume repletion is necessary for correction of the alkalosis. The volume depletion in these patients is caused by losses of sodium and potassium, but the loss of chloride is usually greater than the losses of sodium and potassium combined. Because chloride losses are the dominant cause of the volume depletion, these patients require chloride to correct the volume depletion and metabolic alkalosis; they are said to have chloride-responsive metabolic alkalosis. In contrast, the alkalosis in a patient with an elevated urinary chloride concentration does not respond to volume repletion and is termed chloride-resistant metabolic alkalosis.

Emesis or nasogastric suction results in loss of gastric fluid, which has a high content of HCl. Generation of hydrogen ions by the gastric mucosa causes simultaneous release of bicarbonate into the bloodstream. Normally, the hydrogen ions in gastric fluid are reclaimed in the small intestine (by neutralizing secreted bicarbonate). Thus, there is no net loss of acid. With loss of gastric fluid, this does not occur, and a metabolic alkalosis develops. This period is the generation phase of the metabolic alkalosis.

The maintenance phase of the metabolic alkalosis from gastric losses is due to the volume depletion (“chloride depletion” from gastric loss of HCl). Volume depletion interferes with urinary loss of bicarbonate, the normal renal response to a metabolic alkalosis. During volume depletion, several mechanisms prevent renal bicarbonate loss. First, there is a reduction in the GFR, so less bicarbonate is filtered. Second, volume depletion increases resorption of sodium and bicarbonate in the proximal tubule, limiting the amount of bicarbonate that can be excreted in the urine. This effect is mediated by angiotensin II and by adrenergic stimulation of the kidney, which are both increased in response to volume depletion. Third, the increase in aldosterone during volume depletion increases bicarbonate resorption and hydrogen ion secretion in the collecting duct.

In addition to volume depletion, gastric losses are usually associated with hypokalemia as a result of both gastric loss of potassium and, most importantly, increased urinary potassium losses. The increased urinary losses of potassium are mediated by aldosterone, through volume depletion, and by the increase in intracellular potassium secondary to the metabolic alkalosis, which causes potassium to move into the cells of the kidney, causing increased potassium excretion. Hypokalemia contributes to the maintenance of the metabolic alkalosis by decreasing bicarbonate loss. Hypokalemia increases hydrogen ion secretion in the distal nephron and stimulates ammonia production in the proximal tubule. Ammonia production enhances renal excretion of hydrogen ions.

A metabolic alkalosis can develop in patients receiving loop or thiazide diuretics. Diuretic use leads to volume depletion, which increases angiotensin II, aldosterone, and adrenergic stimulation of the kidney. Diuretics increase the delivery of sodium to the distal nephron, further enhancing acid excretion. Moreover, these diuretics cause hypokalemia, which increases acid excretion by the kidney. The increase in renal acid excretion generates the metabolic alkalosis, and the decrease in bicarbonate loss maintains it. In addition, patients who are receiving diuretics have a “contraction alkalosis.” Diuretic use causes fluid loss without bicarbonate; thus, the remaining body bicarbonate is contained in a smaller total body fluid compartment. The bicarbonate concentration increases, helping to generate the metabolic alkalosis.

Diuretics are often used in patients with edema, such as those with nephrotic syndrome, heart failure, or liver failure. In many of these patients, metabolic alkalosis resulting from diuretic use develops despite the continued presence of edema. This is because the effective intravascular volume is low, and it is the effective intravascular volume that stimulates the compensatory mechanisms that cause and maintain a metabolic alkalosis. Many of these patients have a decreased effective intravascular volume before they begin diuretic therapy, increasing the likelihood of diuretic-induced metabolic alkalosis.

Diuretic use increases chloride excretion in the urine. Consequently, while a patient is receiving diuretics, the urine chloride level is typically

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**Table 55-14 Causes of Metabolic Alkalosis**

<table>
<thead>
<tr>
<th>CHLORIDE-RESPONSIVE (URINARY CHLORIDE &lt;15 mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric losses</td>
</tr>
<tr>
<td>Emesis</td>
</tr>
<tr>
<td>Nasogastric suction</td>
</tr>
<tr>
<td>Diuretics (loop or thiazide)</td>
</tr>
<tr>
<td>Chloride-losing diarrhea (OMIM 214700)</td>
</tr>
<tr>
<td>Chloride-deficient formula</td>
</tr>
<tr>
<td>Cystic fibrosis (OMIM 219700)</td>
</tr>
<tr>
<td>Post-hypercapnia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHLORIDE-RESISTANT (URINARY CHLORIDE &gt;20 mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High blood pressure</td>
</tr>
<tr>
<td>Adrenal adenoma or hyperplasia</td>
</tr>
<tr>
<td>Glucocorticoid-remediable aldosteronism (OMIM 103900)</td>
</tr>
<tr>
<td>Renovascular disease</td>
</tr>
<tr>
<td>Renin-secreting tumor</td>
</tr>
<tr>
<td>17β-Hydroxylase deficiency (OMIM 202110)</td>
</tr>
<tr>
<td>11β-Hydroxylase deficiency (OMIM 202010)</td>
</tr>
<tr>
<td>Cushing syndrome</td>
</tr>
<tr>
<td>11β-Hydroxysteroid dehydrogenase deficiency (OMIM 218030)</td>
</tr>
<tr>
<td>Licorice ingestion</td>
</tr>
<tr>
<td>Liddle syndrome (OMIM 177200)</td>
</tr>
<tr>
<td>Normal blood pressure</td>
</tr>
<tr>
<td>Gitelman syndrome (OMIM 263800)</td>
</tr>
<tr>
<td>Bartter syndrome (OMIM 607364/602522/241200/601678)</td>
</tr>
<tr>
<td>Autosomal dominant hypoparathyroidism (OMIM 146200)</td>
</tr>
<tr>
<td>EAST syndrome (OMIM 612780)</td>
</tr>
<tr>
<td>Base administration</td>
</tr>
</tbody>
</table>

High (>20 mEq/L). After the diuretic effect has worn off, the urinary chloride level is low (<15 mEq/L) owing to appropriate renal chloride retention in response to volume depletion. Thus, categorization of diuretics on the basis of urinary chloride level depends on the timing of the measurement. However, the metabolic alkalosis from diuretics is clearly chloride responsive; it is corrected after adequate volume repletion. This is the rationale for including this process among the chloride-responsive causes of a metabolic alkalosis.

Most patients with diarrhea have a metabolic acidosis as a result of stool losses of bicarbonate. In chloride-losing diarrhea, an autosomal recessive disorder, there is a defect in the normal intestinal exchange of bicarbonate for chloride, causing excessive stool losses of chloride (see Chapter 338). In addition, stool losses of hydrogen ions and potassium cause metabolic alkalosis and hypokalemia, both of which are exacerbated by increased renal hydrogen and potassium losses from volume depletion. Treatment is with oral supplements of potassium and sodium chloride. Use of a gastric proton pump inhibitor, by decreasing gastric HCl production, reduces both the volume of diarrhea and the need for electrolyte supplementation.

An infant formula with extremely low chloride content has led to chloride deficiency and volume depletion. The infants fed this formula, which is no longer available, had a metabolic alkalosis and hypokalemia. Cystic fibrosis can rarely cause metabolic alkalosis, hypokalemia, and hyponatremia because of excessive losses of sodium chloride in sweat (see Chapter 403). The volume depletion causes the metabolic alkalosis and hypokalemia through increased urinary losses, whereas the hyponatremia, a less-common finding, is secondary to sodium loss combined with renal water conservation in an effort to protect the intravascular volume (“appropriate” ADH production).

A posthypercapnic metabolic alkalosis occurs after the correction of a chronic respiratory acidosis. This is typically seen in patients with chronic lung disease who are started on mechanical ventilation. During chronic respiratory acidosis, appropriate renal compensation leads to an increase in the serum bicarbonate concentration. This elevated bicarbonate concentration, because it is still present after acute correction of the respiratory acidosis, causes a metabolic alkalosis. The metabolic alkalosis persists because the patient with a chronic respiratory acidosis is intravascularly depleted because of the chloride loss that occurred during the initial metabolic compensation for the primary respiratory acidosis. In addition, many children with a chronic respiratory acidosis receive diuretics, which further decrease the intravascular volume. The metabolic alkalosis responds to correction of the intravascular volume deficit.

The chloride-resistant causes of metabolic alkalosis can be subdivided according to blood pressure status. Patients with hypertension either have increased aldosterone levels or act as if they do. Aldosterone levels are elevated in children with adenal adenomas or hyperplasia. Aldosterone causes renal retention of sodium, with resultant hypertension. Metabolic alkalosis and hypokalemia result from aldosterone-mediated renal excretion of hydrogen ions and potassium. The urinary chloride level is not low because these patients are volume-overloaded, not volume-depleted. The volume expansion and hypertension allow normal excretion of sodium and chloride despite the presence of aldosterone. This is known as the mineralocorticoid escape phenomenon.

In glucocorticoid-remediable aldosteronism, an autosomal dominant disorder, there is excess production of aldosterone owing to the presence of an aldosterone synthase gene that is regulated by adrenocorticotropic hormone (ACTH) (see Chapter 576.8). Glucocorticoids effectively treat this disorder by inhibiting ACTH production by the pituitary, downregulating the inappropriate aldosterone production. Renovascular disease and renin-secreting tumors both cause excessive renin, leading to an increase in aldosterone, although hypokalemia and metabolic alkalosis are less-common findings than hypertension. In 2 forms of congenital adrenal hyperplasia, 11β-hydroxylase deficiency and 17α-hydroxylase deficiency, there is excessive production of the mineralocorticoid 11-deoxycorticosterone (see Chapters 576.2 and 576.4). Hypertension, hypokalemia, and metabolic alkalosis are more likely in 17α-hydroxylase deficiency than in 11β-hydroxylase deficiency. These disorders respond to glucocorticoids because the excess production of 11-deoxycorticosterone is under the control of ACTH.

Cushing syndrome frequently causes hypertension. Cortisol has some mineralocorticoid activity, and high levels can produce hypokalemia and metabolic alkalosis in patients with Cushing syndrome. Cortisol can bind to the mineralocorticoid receptors in the kidney and function as a mineralocorticoid. This binding normally does not occur because 11β-hydroxysteroid dehydrogenase in the kidney converts cortisol to cortisone, which does not bind to the mineralocorticoid receptor. In 11β-hydroxysteroid dehydrogenase deficiency, also called apparent mineralocorticoid excess, cortisol is not converted in the kidney to cortisone. Cortisol is therefore available to bind to the mineralocorticoid receptor in the kidney and act as a mineralocorticoid. Patients with this deficiency, despite low levels of aldosterone, are hypertensive and hypokalemic, and they have a metabolic alkalosis. The same phenomenon can occur with excessive intake of natural licorice, a component of which, glycyrrhizic acid, inhibits 11β-hydroxysteroid dehydrogenase. The autosomal dominant disorder Liddle syndrome is secondary to an activating mutation of the sodium channel in the distal nephron (see Chapter 531.3). Upregulation of this sodium channel is one of the principal actions of aldosterone. Because this sodium channel is continuously open, children with Liddle syndrome have the features of hyperaldosteronism, including hypertension, hypokalemia, and metabolic alkalosis, but low serum levels of aldosterone.

Bartter syndrome and Gitelman syndrome are autosomal recessive disorders associated with normal blood pressure, elevations of urinary chloride, metabolic alkalosis, and hypokalemia (see Chapter 531). In Bartter syndrome, patients have a defect in sodium and chloride resorption in the loop of Henle. This leads to excessive urinary losses of sodium and chloride, and as in patients receiving loop diuretics, volume depletion and secondary hyperaldosteronism occur, causing hypokalemia and metabolic alkalosis. Gitelman syndrome is usually milder than Bartter syndrome. Patients have renal sodium and chloride wasting with volume depletion due mutations in the gene encoding the thiazide-sensitive sodium-chloride transporter in the distal tubule. As in patients receiving a thiazide diuretic, affected patients have volume depletion and secondary hyperaldosteronism with hypokalemia and metabolic alkalosis. Children with Gitelman syndrome have hypocalciuria and hypomagnesemia. Some patients with autosomal dominant hypoparathyroidism have hypokalemia and metabolic alkalosis due to impaired sodium and chloride resorption in the loop of Henle. EAST syndrome causes hypokalemia, metabolic alkalosis and hypomagnesemia.

Excessive base intake can cause a metabolic alkalosis. Affected patients do not have a low urine chloride level, unless there is associated volume depletion. In the absence of volume depletion, excess base is rapidly corrected via renal excretion of bicarbonate. Rarely, massive base intake can cause a metabolic alkalosis by overwhelming the kidney’s ability to excrete bicarbonate. This may occur in infants who are given baking soda as a “home remedy” for colic or stomach upset. Each teaspoon of baking soda has 42 mEq of sodium bicarbonate. Infants have increased vulnerability because of a lower GFR, limiting the rate of compensatory renal bicarbonate excretion. A metabolic alkalosis may also occur in patients who receive a large amount of sodium bicarbonate during cardiopulmonary resuscitation. Blood products are anticoagulated with citrate, which is converted into bicarbonate by the liver. Patients who receive large amounts of blood products may have a metabolic alkalosis. Latrogenic metabolic alkalosis can occur as a result of acetate in total parenteral nutrition. Aggressive use of bicarbonate therapy in a child with a lactic acidosis or diabetic ketoacidosis may cause a metabolic alkalosis. This event is especially likely in a patient in whom the underlying cause of the lactic acidosis is successfully corrected (restoration of intravascular volume in a patient with severe dehydration). Once the cause of the lactic acidosis resolves, lactate can be converted by the liver into bicarbonate, which when combined with infused bicarbonate can create a metabolic alkalosis. A similar phenomenon can occur in a child with diabetic ketoacidosis.
because the administration of insulin allows keto acids to be metabolized, producing bicarbonate. However, this phenomenon rarely occurs because of judicious use of bicarbonate therapy in diabetic ketoacidosis and because there are usually significant pretreatment losses of keto acids in the urine, preventing massive regeneration of bicarbonate. Base administration is most likely to cause a metabolic alkalosis in patients who have an impaired ability to excrete bicarbonate in the urine. This impairment occurs in patients with concurrent volume depletion or renal insufficiency.

**Clinical Manifestations**

The symptoms in patients with a metabolic alkalosis are often related to the underlying disease and associated electrolyte disturbances. Children with chloride-responsive causes of metabolic alkalosis often have symptoms related to volume depletion, such as thirst and lethargy. In contrast, children with chloride-unresponsive causes may have symptoms related to hypertension.

Alkalemia causes potassium to shift into the intracellular space, producing a decrease in the extracellular potassium concentration. Alkalemia leads to increased urinary losses of potassium. Increased potassium losses are present in many of the conditions that cause a metabolic alkalosis. Therefore, most patients with a metabolic alkalosis have hypokalemia, and their symptoms may be related to the hypokalemia (see Chapter 55.4).

The symptoms of a metabolic alkalosis are caused by the associated alkalemia. The magnitude of the alkalemia is related to the severity of the metabolic alkalosis and the presence of concurrent respiratory acid–base disturbances. During alkalemia, the ionized calcium concentration decreases as a result of increased binding of calcium to albumin. The decrease in the ionized calcium concentration may cause symptoms of *tetany* (carpopedal spasm).

Arrhythmias are a potential complication of a metabolic alkalosis, and the risk for arrhythmia increases if there is concomitant hypokalemia. Alkalemia increases the risk of digoxin toxicity, and antiarrhythmic medications are less effective in the presence of alkalemia. In addition, alkalemia may decrease cardiac output. A metabolic alkalosis causes a compensatory increase in the Pco₂ by decreasing ventilation. In patients with underlying lung disease, the decrease in ventilatory drive can cause hypoxia. In patients with normal lungs, the hypoventilation seen in severe metabolic alkalosis can cause hypoxia.

**Diagnosis**

Measurement of the urinary chloride concentration is the most helpful test in differentiating among the causes of a metabolic alkalosis. The urine chloride level is low in patients with a metabolic alkalosis resulting from volume depletion, whereas there is a defect in renal handling of chloride. The urine chloride level is superior to the urine sodium level in assessment of volume status in patients with a metabolic alkalosis, because the normal renal response to a metabolic alkalosis is to excrete bicarbonate. Because bicarbonate is negatively charged, it can be excreted only with a cation, usually sodium and potassium. Hence, a patient with a metabolic alkalosis may excrete sodium in the urine despite the presence of volume depletion, which normally causes avid sodium retention. The *urine chloride level is usually a good indicator of volume status, and it differentiates among the chloride-resistant and chloride-responsive causes of a metabolic alkalosis.*

Diuretics and gastric losses are the most common causes of metabolic alkalosis and are usually readily apparent from the patient history. Occasionally, metabolic alkalosis, usually with hypokalemia, may be a clue to the presence of bulimia or surreptitious diuretic use (see Chapter 28). Patients with bulimia have a low urine chloride level, indicating that they have volume depletion as a result of an extrarenal etiology, but there is no alternative explanation for their volume depletion. Surreptitious diuretic use may be diagnosed by obtaining a urine toxicology screen for diuretics. The urine chloride level is increased while a patient is using diuretics but is low when the patient stops taking them. Rarely, children with mild Bartter syndrome or Gitelman syndrome are misdiagnosed as having bulimia or abusing diuretics.

The urine chloride value is always elevated in Bartter syndrome and Gitelman syndrome, and the urine toxicology screen for diuretics has a negative result. Metabolic alkalosis with hypokalemia is occasionally the initial manifestation of cystic fibrosis. An elevated sweat chloride finding is diagnostic.

Patients with a metabolic alkalosis and a high urinary chloride level are subdivided according to blood pressure status. Children with normal blood pressure may have Bartter syndrome or Gitelman syndrome. Excess base administration is another diagnostic possibility, but it is usually apparent from the history. In patients with sodium bicarbonate ingestion (baking soda), which may be unreported by the parent, the metabolic alkalosis usually occurs with significant hypernatremia. In addition, unless volume depletion is superimposed, the metabolic alkalosis from base ingestion resolves itself once the source of base is eliminated.

Measuring serum concentrations of renin and aldosterone differentiates children with a metabolic alkalosis, a high urinary chloride level, and elevated blood pressure. Both renin and aldosterone are elevated in children with either renovascular disease or a renin-secreting tumor. Aldosterone is high and renin is low in patients with adrenal adenomas or hyperplasia and glucocorticoid-remediable aldosteronism. Renin and aldosterone are low in children with Cushing syndrome; Liddle syndrome, licorice ingestion, 17α-hydroxylase deficiency, 1ββ-hydroxylase deficiency, and 11β-hydroxysteroid dehydrogenase deficiency. An elevated 24 hr urine cortisol value is diagnostic of Cushing syndrome, which is suspected from the presence of the other classic features of this disease (see Chapter 577). Elevations of 11-deoxycorticosterone values are seen in 17α-hydroxylase deficiency and 11β-hydroxylase deficiency.

**Treatment**

The approach to treatment of metabolic alkalosis depends on the severity of the alkalosis and the underlying etiology. In children with a mild metabolic alkalosis ([HCO₃⁻] <32), intervention is often unnecessary, although this depends on the specific circumstances. In a child with congenital heart disease who is receiving a stable dose of a loop diuretic, a mild alkalosis does not require treatment. In contrast, intervention may be appropriate in a child with a worsening mild metabolic alkalosis because of nasogastric suction. The presence of a concurrent respiratory acid–base disturbance also influences therapeutic decision making. A patient with a concurrent respiratory acidosis should have some increase in bicarbonate owing to metabolic compensation; thus, the severity of the pH elevation is more important than the bicarbonate concentration. In contrast, a patient with a respiratory alkalosis and a metabolic alkalosis is at risk for severe alkalosis; treatment may be indicated, even if the increase in bicarbonate value is only mild.

Intervention is usually necessary in children with moderate or severe metabolic alkalosis. The most effective approach is to address the underlying etiology. In some children, nasogastric suction may be decreased or discontinued. Alternatively, the addition of a gastric proton pump inhibitor reduces gastric secretion and losses of HCl. Diuretics are an important cause of metabolic alkalosis, and if a change is tolerated, they should be eliminated or the dose reduced. Adequate potassium supplementation or the addition of a potassium-sparring diuretic is also helpful in a child with a metabolic alkalosis from diuretics. Potassium-sparring diuretics not only decrease renal potassium losses but, by blocking the action of aldosterone, also decrease hydrogen ion secretion in the distal nephron, increasing urinary bicarbonate excretion. Many children cannot tolerate discontinuation of diuretic therapy; thus, potassium supplementation and potassium-sparring diuretics are the principal therapeutic approach. Arginine HCl may also be used to treat chloride-responsive metabolic acidosis if sodium or potassium salts are not appropriate. Arginine HCl may raise the serum potassium levels during administration. Rarely, in cases of severe metabolic alkalosis, acetazolamide is an option. A carbonic anhydrase inhibitor, acetazolamide decreases resorption of bicarbonate in the proximal tubule, causing significant bicarbonate loss in the urine. The patient receiving this drug must be monitored closely,
because acetazolamide produces major losses of potassium in the urine and increases fluid losses, potentially necessitating a reduction in dosage of other diuretics.

Most children with a metabolic alkalosis have one of the chloride-responsive etiologies. In these situations, administration of sufficient sodium chloride and potassium chloride to correct the volume deficit and the potassium deficit is necessary to correct the metabolic alkalosis. This approach may not be an option in the child who has volume depletion due to diuretics, because volume repletion may be contraindicated. Adequate replacement of gastric losses of sodium and potassium in a child with a nasogastric tube can minimize or prevent the development of the metabolic alkalosis. With adequate intravascular volume and a normal serum potassium concentration, the kidney is able to excrete the excess bicarbonate within a couple of days.

In children with the chloride-resistant causes of a metabolic alkalosis that are associated with hypertension, volume repletion is contraindicated because it would exacerbate the hypertension and would not repair the metabolic alkalosis. Ideally, treatment focuses on eliminating the excess aldosterone effect. Adrenal adenomas can be resected, licorice intake can be eliminated, and renovascular disease can be repaired. Glucocorticoid-remediable aldosteronism, 17α-hydroxylase deficiency, and 11β-hydroxylase deficiency respond to the administration of glucocorticoids. The mineralocorticoid effect of cortisol in 11β-hydroxysteroid dehydrogenase deficiency can be decreased with the use of spironolactone, which blocks the mineralocorticoid receptor.

In contrast, the metabolic alkalosis in children with Liddle syndrome does not respond to spironolactone; however, either triamterene or amiloride is effective therapy because both agents block the sodium channel that is constitutively active in Liddle syndrome.

In children with Bartter syndrome and Gitelman syndrome, therapy includes oral potassium supplementation and potassium-sparring diuretics. Children with Gitelman syndrome often require magnesium supplementation, whereas children with severe Bartter syndrome often benefit from indomethacin.

**RESPIRATORY ACIDOSIS**

A respiratory acidosis is an inappropriate increase in blood CO₂ (PCO₂). Carbon dioxide is a byproduct of metabolism, and it is removed from the body by the lungs. During a respiratory acidosis, there is a decrease in the effectiveness of CO₂ removal by the lungs. A respiratory acidosis is secondary to either pulmonary disease, such as severe bronchiolitis, or nonpulmonary disease, such as a narcotic overdose. Even though body production of CO₂ can vary, normal lungs are able to accommodate this variation; excess production of CO₂ is not an isolated cause of a respiratory acidosis. With impairment of alveolar ventilation, the rate of body production of CO₂ may affect the severity of the respiratory acidosis, but this is usually not a significant factor.

A respiratory acidosis causes a decrease in the blood pH, but there is normally a metabolic response that partially compensates, minimizing the severity of the acidemia. The acute metabolic response to a respiratory alkalosis occurs within minutes. The metabolic compensation for an acute respiratory acidosis is secondary to titration of acid by nonbicarbonate buffers. This buffering of hydrogen ions causes a predictable increase in the serum bicarbonate concentration: Plasma bicarbonate increases by 1 for each 10 mm Hg increase in the PCO₂ (acute compensation).

With a chronic respiratory acidosis, there is more significant metabolic compensation and, thus, less severe acidemia than in an acute respiratory acidosis with the same increase in PCO₂. During a chronic respiratory acidosis, the kidneys increase acid excretion. This response occurs over 3-4 days and causes a predictable increase in the serum bicarbonate concentration: Plasma bicarbonate increases by 3.5 for each 10 mm Hg increase in the PCO₂ (chronic compensation).

The increase of serum bicarbonate concentration during a chronic respiratory acidosis is associated with a decrease in body chloride. After acute correction of a chronic respiratory acidosis, the plasma bicarbonate continues to be increased, and the patient has a metabolic alkalosis. Because of the chloride deficit, this is a chloride-responsive metabolic alkalosis; it corrects once the patient’s chloride deficit is replaced.

A mixed disorder is present if the metabolic compensation is inappropriate. A higher-than-expected bicarbonate value occurs in the setting of a concurrent metabolic alkalosis, and a lower-than-expected bicarbonate value occurs in the setting of a concurrent metabolic acidoisis. Evaluating whether compensation is appropriate during a respiratory acidosis requires clinical knowledge of the acuity of the process, because the expected compensation is different, depending on whether the process is acute or chronic.

The PCO₂ cannot be interpreted in isolation to determine whether a patient has a respiratory acidosis. A respiratory acidosis is always present if a patient has acidemia and an elevated PCO₂. However, an elevated PCO₂ also occurs as appropriate respiratory compensation for a simple metabolic alkalosis. The patient is alkalemic; this is not a respiratory acidosis. During a mixed disturbance, a patient can have a respiratory acidosis and a normal or even low PCO₂. This condition may occur in a patient with a metabolic acidosis; a respiratory acidosis is present if the patient does not have appropriate respiratory compensation (the PCO₂ is higher than expected from the severity of the metabolic acidosis).

**Etiology and Pathophysiology**

The causes of a respiratory acidosis are either pulmonary or nonpulmonary (Table 55-15). CNS disorders can decrease the activity of the central respiratory center, reducing ventilatory drive. A variety of medications and illicit drugs suppress the respiratory center. The signals from the respiratory center need to be transmitted to the respiratory muscles via the nervous system. Respiratory muscle failure can be secondary to disruption of the signal from the CNS in the spinal cord, the phrenic nerve, or the neuromuscular junction. Disorders directly affecting the muscles of respiration can prevent adequate ventilation, causing a respiratory acidosis.

Mild or moderate lung disease often causes a respiratory alkalosis as a result of hyperventilation secondary to hypoxia or stimulation of lung mechanoreceptors or chemoreceptors. Only more severe lung disease causes a respiratory acidosis. Upper airway diseases, by impairing air entry into the lungs, may decrease ventilation, producing a respiratory acidosis.

Increased production of CO₂ is never the sole cause of a respiratory acidosis, but it can increase the severity of the disease in a patient with decreased ventilation of CO₂. Increased production of CO₂ occurs in patients with fever, hyperthyroidism, excess caloric intake, and high levels of physical activity. Increased respiratory muscle work also increases CO₂ production.

**Clinical Manifestations**

Patients with a respiratory acidosis are often tachypneic in an effort to correct the inadequate ventilation. Exceptions include patients with a respiratory acidosis resulting from CNS depression and patients who are on the verge of complete respiratory failure secondary to fatigue of the respiratory muscles.

The symptoms of respiratory acidosis are related to the severity of the hypercarbia. Acute respiratory acidosis is usually more symptomatic than chronic respiratory acidosis. Symptoms are also increased by concurrent hypoxia or metabolic acidosis. In a patient breathing room air, hypoxia is always present if a respiratory acidosis is present. The potential CNS manifestations of respiratory acidosis include anxiety, dizziness, headache, confusion, asterixis, myoclonic jerks, hallucinations, psychosis, coma, and seizures.

Acidemia, no matter the etiology, affects the cardiovascular system. An arterial pH < 7.2 impairs cardiac contractility and the normal response to catecholamines, in both the heart and the peripheral vasculature. Hypercapnia causes vasodilation, most dramatically in the cerebral vasculature, but hypercapnia produces vasoconstriction of the pulmonary circulation. Respiratory acidosis increases the risk of cardiac arrhythmias, especially in a child with underlying cardiac disease.
Causes of Respiratory Acidosis

<table>
<thead>
<tr>
<th>Table 55-15</th>
<th>Causes of Respiratory Acidosis</th>
</tr>
</thead>
</table>
| **CENTRAL NERVOUS SYSTEM DEPRESSION** | Encephalitis  
Head trauma  
Brain tumor  
Central sleep apnea  
Primary pulmonary hypoventilation (Ondine curse)  
Stroke  
Hyponic brain damage  
Obesity-hypoventilation (Pickwickian syndrome)  
Increased intracranial pressure |
| **Medications** | Narcotics  
Barbiturates  
Anesthesia  
Benzodiazepines  
Propofol  
Alcohols |
| **DISORDERS OF THE SPINAL CORD, PERIPHERAL NERVES, OR NEUROMUSCULAR JUNCTION** | Diaphragmatic paralysis  
Guillain-Barré syndrome  
Poliomyelitis  
Spinal muscular atrophies  
Tick paralysis  
Botulism  
Myasthenia  
Multiple sclerosis  
Spinal cord injury  
Medications  
Vercenium  
Aminoglycosides  
Organophosphates (pesticides) |
| **RESPIRATORY MUSCLE WEAKNESS** | Muscular dystrophy  
Hypothyroidism  
Malnutrition  
Hypokalemia  
Hypophosphatemia  
Medications  
Sucinylcholine  
Corticosteroids |
| **PULMONARY DISEASE** | Pneumonia  
Pneumothorax  
Asthma  
Bronchiolitis  
Pulmonary edema  
Pulmonary hemorrhage  
Acute respiratory distress syndrome  
Neonatal respiratory distress syndrome  
Cystic fibrosis  
Bronchopulmonary dysplasia  
Hyplasatic lungs  
Meconium aspiration  
Pulmonary thromboembolus  
Interstitial fibrosis |
| **UPPER AIRWAY DISEASE** | Aspiration  
Laryngospasm  
Angieoedema  
Obstructive sleep apnea  
Tonsillar hypertrophy  
Vocal cord paralysis  
Extrinsic tumor  
Extrinsic or intrinsic hemangioma |
| **MISCELLANEOUS** | Flail chest  
Cardiac arrest  
Kyphoscoliosis  
Decreased diaphragmatic movement due to ascites or peritoneal dialysis |

Diagnosis

The history and physical findings often point to a clear etiology. For the obtunded patient with poor respiratory effort, evaluation of the CNS is often indicated. This may include imaging studies (CT or MRI) and, potentially, a lumbar puncture for cerebrospinal fluid analysis. A toxicology screen for illicit drugs may also be appropriate. A response to naloxone is both diagnostic and therapeutic. In many of the diseases affecting the respiratory muscles, there is evidence of weakness in other muscles. Strider is a clue that the child may have upper airway disease. Along with a physical examination, a chest radiograph is often helpful in diagnosing pulmonary disease.

In many patients, respiratory acidosis may be multifactorial. A child with bronchopulmonary dysplasia, an intrinsic lung disease, may worsen because of respiratory muscle dysfunction caused by severe hypokalemia resulting from long-term diuretic therapy. Conversely, a child with muscular dystrophy, a muscle disease, may worsen because of aspiration pneumonia.

For a patient with respiratory acidosis, calculation of the gradient between the alveolar oxygen concentration and the arterial oxygen concentration, the A–A \(O_2\) gradient, is useful for distinguishing between poor respiratory effort and intrinsic lung disease. The A–A \(O_2\) gradient is increased if the hypoxemia is caused by intrinsic lung disease (see Chapter 373). Treatment

Respiratory acidosis is best managed by treatment of the underlying etiology. In some instances, the response is very rapid, such as after the administration of naloxone to a patient with a narcotic overdose. In contrast, in the child with pneumonia, a number of days of antibiotic therapy may be required before the respiratory status improves. In many children with a chronic respiratory acidosis, there is no curative therapy, although an acute respiratory illness superimposed on a chronic respiratory condition is usually reversible.

All patients with an acute respiratory acidosis are hypoxic, and therefore need to receive supplemental oxygen. Mechanical ventilation is necessary in some children with a respiratory acidosis. Children with a significant respiratory acidosis caused by a CNS disease usually require mechanical ventilation because such a disorder is unlikely to respond quickly to therapy. In addition, hypercarbia causes cerebral vasodilation, and the increase in intracranial pressure can be dangerous in a child with an underlying CNS disease. Readily reversible CNS depression, such as from a narcotic overdose, may not require mechanical ventilation. Decisions on mechanical ventilation for other patients depend on a number of factors. Patients with severe hypercarbia—\(P_{CO_2} > 75\) mm Hg—usually require mechanical ventilation (see Chapter 71). The threshold for intubation is lower if there is concomitant metabolic acidosis, a slowly responsive underlying disease, or hypoxia that responds poorly to oxygen, or if the patient appears to be tiring and respiratory arrest seems likely.

In patients with a chronic respiratory acidosis, the respiratory drive is often less responsive to hypercarbia and more responsive to hypoxia. Hence, with chronic respiratory acidosis, excessive use of oxygen can blunt the respiratory drive and therefore increase the \(P_{CO_2}\). In these patients, oxygen must be used cautiously.

When possible, it is best to avoid mechanical ventilation in a patient with a chronic respiratory acidosis because extubation is often difficult. However, an acute illness may necessitate mechanical ventilation in a child with a chronic respiratory acidosis. When intubation is necessary, the \(P_{CO_2}\) should be lowered only to the patient’s normal baseline, and this should be done gradually. These patients normally have an elevated serum bicarbonate concentration as a result of metabolic compensation for their respiratory acidosis. A rapid lowering of the \(P_{CO_2}\) can cause a severe metabolic alkalosis, potentially leading to complications, including cardiac arrhythmias, decreased cardiac output, and decreased cerebral blood flow. In addition, prolonged mechanical ventilation at a normal \(P_{CO_2}\) causes the metabolic compensation to resolve. When the patient is subsequently extubated, the patient will no longer benefit from metabolic compensation, causing a more severe acidemia because of the respiratory acidosis.
**RESPIRATORY ALKALOSIS**

A respiratory alkalosis is an inappropriate reduction in the blood CO₂ concentration. This is usually secondary to hyperventilation, initially causing removal of CO₂ to surpass production. Eventually, a new steady state is achieved, with removal equaling production, albeit at a lower CO₂ tension (Pco₂). A respiratory alkalosis that is not the result of hyperventilation may occur in children receiving extracorporeal membrane oxygenation or hemodialysis, with CO₂ lost directly from the blood in the extracorporeal circuit.

With a simple respiratory alkalosis, the pH increases but there is a normal metabolic response that attenuates some of the change in the blood pH. A metabolic response to an acute respiratory alkalosis occurs within minutes, mediated by hydrogen ion release from nonbicarbonate buffers. The metabolic response to an acute respiratory alkalosis is predictable: Plasma bicarbonate falls by 2 for each 10 mm Hg decrease in the Pco₂ (acute compensation).

A chronic respiratory alkalosis leads to more significant metabolic compensation because of the actions of the kidneys, which decrease acid secretion, producing a decrease in the serum bicarbonate concentration. Both the proximal and distal tubules decrease acid secretion. Metabolic compensation for a respiratory alkalosis develops gradually and takes 2-3 days to produce the full effect: Plasma bicarbonate falls by 4 for each 10 mm Hg decrease in the Pco₂ (chronic compensation).

A chronic respiratory alkalosis is the only acid–base disturbance wherein appropriate compensation may normalize the pH, albeit >7.4.

A mixed disorder is present if the metabolic compensation is inappropriate. A higher than expected bicarbonate level occurs in the setting of a concurrent metabolic alkalosis, and a lower than expected bicarbonate level occurs in the setting of a concurrent metabolic acidosis. Evaluating whether compensation is appropriate during a respiratory alkalosis requires clinical knowledge of the acuity of the process, because the expected compensation differs according to whether the process is acute or chronic.

A low Pco₂ value does not always indicate a respiratory alkalosis. The Pco₂ also decreases as part of the appropriate respiratory compensation for a metabolic acidosis; this is not a respiratory alkalosis. A metabolic acidosis is the dominant acid–base disturbance in a patient with acidemia and a low Pco₂, even though there could still be a concurrent respiratory alkalosis. In contrast, a respiratory alkalosis is always present in a patient with alkalemia and a low Pco₂. Even a normal Pco₂ value may be consistent with a respiratory alkalosis in a patient with a metabolic alkalosis because an elevated Pco₂ is expected as part of appropriate respiratory compensation for the metabolic alkalosis.

**Etiology and Pathophysiology**

A variety of stimuli can increase the ventilatory drive and cause a respiratory alkalosis (Table 55-16). Arterial hypoxemia or tissue hypoxia stimulates peripheral chemoreceptors to signal the central respiratory center in the medulla to increase ventilation. The resultant greater respiratory effort increases the oxygen content of the blood but depresses the Pco₂. The effect of hypoxemia on ventilation begins when the oxygen saturation decreases to approximately 90% (Po₂ = 60 mm Hg), and hyperventilation increases as hypoxemia worsens. Acute hypoxia is a more potent stimulus for hyperventilation than chronic hypoxia; thus, chronic hypoxia, as occurs in cyanotic heart disease, causes a much-less-severe respiratory alkalosis than an equivalent degree of acute hypoxia. There are many causes of hypoxemia or tissue hypoxia, including primary lung disease, severe anemia, and carbon monoxide poisoning.

The lungs contain chemoreceptors and mechanoreceptors that respond to irritants and stretching and send signals to the respiratory center to increase ventilation. Aspiration or pneumonia may stimulate the chemoreceptors, whereas pulmonary edema may stimulate the mechanoreceptors. Most of the diseases that activate these receptors may also cause hypoxemia and can, therefore, potentially lead to hyperventilation via 2 mechanisms. Patients with primary lung disease may initially have a respiratory alkalosis, but worsening of the disease, combined with respiratory muscle fatigue, often causes respiratory failure and the development of a respiratory acidosis.

**Hyperventilation in the absence of lung disease** occurs with direct stimulation of the central respiratory center. This occurs with CNS diseases, such as meningitis, hemorrhage, and trauma. Central hyperventilation due to lesions, such as infarcts or tumors near the central respiratory center in the midbrain, increases the rate and depth of the respiratory effort. This respiratory pattern portends a poor prognosis because these midbrain lesions are frequently fatal. Systemic processes may cause centrally mediated hyperventilation. Although the exact mechanisms are not clear, liver disease causes a respiratory alkalosis that is usually proportional to the degree of liver failure. Pregnancy causes a chronic respiratory alkalosis, probably mediated by progesterone acting on the respiratory centers. Salicylates, although often causing a concurrent metabolic acidosis, directly stimulate the respiratory center to produce a respiratory alkalosis. The respiratory alkalosis during sepsis is probably due to cytokine release.

**Hyperventilation may be secondary to an underlying disease** that causes pain, stress, or anxiety. In psychogenic hyperventilation or in panic attacks, there is no disease process accounting for the hyperventilation. This disorder may occur in a child who has had an emotionally stressful experience. Alternatively, it may be part of a panic disorder,
Although lung disease is often apparent by history or physical examination, a chest radiograph may detect more subtle disease. The patient with a pulmonary embolism may have benign chest radiograph findings, normal pO₂, and isolated respiratory alkalosis, although hypoxia may eventually occur. Diagnosis of a pulmonary embolism requires a high index of suspicion and should be considered in children without another explanation for respiratory alkalosis, especially if risk factors are present, such as prolonged bed rest and a hypercoagulable state (e.g., nephrotic syndrome or lupus anticoagulant).

### Treatment

There is seldom a need for specific treatment of respiratory alkalosis. Rather, treatment focuses on the underlying disease. Mechanical ventilator settings are adjusted to correct iatrogenic respiratory alkalosis, unless the hyperventilation has a therapeutic purpose (e.g., treatment of increased intracranial pressure).

For the patient with hyperventilation secondary to anxiety, efforts should be undertaken to reassure the child, usually enlisting the parents. Along with reassurance, patients with psychogenic hyperventilation may benefit from benzodiazepines. During an acute episode of psychogenic hyperventilation, rebreathing into a paper bag increases the patient’s PCO₂. Using a paper bag, instead of a plastic bag, allows adequate oxygenation but permits the CO₂ concentration in the bag to increase. The resultant increase in the patient’s PCO₂ decreases the symptoms of the respiratory alkalosis that tend to perpetuate the hyperventilation. Rebreathing should be performed only once other causes of hyperventilation have been eliminated; pulse oximetry during the rebreathing is prudent.

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Maintenance and Replacement Therapy
Larry A. Greenbaum

Maintenance intravenous fluids are used in a child who cannot be fed enterally. Along with maintenance fluids, children may require concurrent replacement fluids if they have continued excessive losses, such as may occur with drainage from a nasogastric (NG) tube or with high urine output because of nephrogenic diabetes insipidus. If dehydration is present, the patient also needs to receive deficit replacement (see Chapter 57). A child awaiting surgery may need only maintenance fluids, whereas a child with diarrheal dehydration needs maintenance and deficit therapy and also may require replacement fluids if significant diarrhea continues.

**MAINTENANCE THERAPY**
Children normally have large variations in their daily intake of water and electrolytes. The only exceptions are patients who receive fixed dietary regimens orally, via a gastric tube, or as intravenous total parenteral nutrition (TPN). Healthy children can tolerate significant variations in intake because of the many homeostatic mechanisms that can adjust absorption and excretion of water and electrolytes (see Chapter 55). The calculated water and electrolyte needs that form the basis of maintenance therapy are not absolute requirements. Rather, these calculations provide reasonable guidelines for a starting point to estimate intravenous therapy. Children do not need to be started on intravenous fluids simply because their intake is being monitored in a hospital and they are not taking "maintenance fluids" orally, unless there is a pathologic process present that necessitates high fluid intake.
Maintenance fluids are most commonly necessary in preoperative and postoperative surgical patients; many nonsurgical patients also require maintenance fluids. It is important to recognize when it is necessary to begin maintenance fluids. A normal teenager who is given nothing by mouth (NPO) overnight for a morning procedure does not require maintenance fluids because a healthy adolescent can easily tolerate 12 or 18 hr without oral intake. In contrast, a 6 mo old child waiting for surgery should begin receiving intravenous fluids within 8 hr of the last feeding. Infants become dehydrated more quickly than older patients. A child with obligatory high urine output from nephrogenic diabetes insipidus should begin receiving intravenous fluids soon after being classified as NPO.

Maintenance fluids are composed of a solution of water, glucose, sodium, and potassium. This solution has the advantages of simplicity, long shelf life, low cost, and compatibility with peripheral intravenous administration. Such a solution accomplishes the major objectives of maintenance fluids (Table 56-1). Patients lose water, sodium, and potassium in their urine and stool; water is also lost from the skin and lungs. Maintenance fluids replace these losses, thereby avoiding the development of dehydration and deficiency of sodium or potassium. The glucose in maintenance fluids provides approximately 20% of the normal caloric needs of the patient, prevents the development of starvation ketoacidosis, and diminishes the protein degradation that would occur if the patient received no calories. Glucose also provides added osmotes, thus avoiding the administration of hypotonic fluids that may cause hemolysis.

Maintenance fluids do not provide adequate calories, protein, fat, minerals, or vitamins. This fact is typically not problematic for a patient receiving intravenous fluids for a few days. A patient receiving maintenance intravenous fluids is receiving inadequate calories and will lose 0.5-1% of weight each day. It is imperative that patients not remain on maintenance therapy indefinitely; TPN should be used for children who cannot be fed enterally for more than a few days, especially patients with underlying malnutrition.

Prototypical maintenance fluid therapy does not provide electrolytes such as calcium, phosphorus, magnesium, and bicarbonate. For most patients, this lack is not problematic for a few days, although there are patients who will not tolerate this omission, usually because of excessive losses. A child with renal tubular acidosis wastes bicarbonate in urine. Such a patient will rapidly become acidic unless bicarbonate (or acetate) is added to the maintenance fluids. It is important to remember the limitations of maintenance fluid therapy.

### MAINTENANCE WATER

Water is a crucial component of maintenance fluid therapy because of the obligatory daily water losses. These losses are both measurable (urine, stool) and not measurable (insensible losses from the skin and lungs). Failure to replace these losses leads to a child who is thirsty, uncomfortable, and, ultimately, dehydrated.

The goal of maintenance water is to provide enough water to replace these losses. Although urinary losses are approximately 60% of the total, the normal kidney has the ability to markedly modify water losses, with daily urine volume potentially varying by more than a factor of 20. Maintenance water is designed to provide enough water so that the kidney does not need to significantly dilute or concentrate the urine. It also provides a margin of safety, so that normal homeostatic mechanisms can adjust urinary water losses to prevent overhydration and dehydration. This adaptability obviates the need for absolute precision in determining water requirements. This fact is important, given the absence of absolute accuracy in the formulas for calculation of water needs.

<table>
<thead>
<tr>
<th>Table 56-1</th>
<th>Goals of Maintenance Fluids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevent dehydration</td>
<td></td>
</tr>
<tr>
<td>Prevent electrolyte disorders</td>
<td></td>
</tr>
<tr>
<td>Prevent ketoacidosis</td>
<td></td>
</tr>
<tr>
<td>Prevent protein degradation</td>
<td></td>
</tr>
</tbody>
</table>

Table 56-2 provides a system for calculating maintenance water on the basis of the patient’s weight and emphasizes the high water needs of smaller, less-mature patients. This approach is reliable, although calculations based on weight do overestimate the water needs of an overweight child, in whom it is better to base the calculations on the lean body weight, which can be estimated by using the 50th percentile of body weight for the child’s height. It is also important to remember that there is an upper limit of 2.4 L/24 hr in adult-sized patients. Intravenous fluids are written as an hourly rate. The formulas in Table 56-3 enable rapid calculation of the rate of maintenance fluids.

### INTRAVENOUS SOLUTIONS

The components of the commonly available solutions are shown in Table 56-4. Normal saline (NS) and Ringer lactate (LR) are isotonic solutions; they have approximately the same tonicity as plasma. Isotonic fluids without glucose are used for the acute correction of intravascular volume depletion (see Chapter 57). The usual choices for maintenance fluid therapy in children are half-normal saline (1/2 NS) and NS. These solutions are available with 5% dextrose (D5) or without dextrose. In addition, they are available with 20 mEq/L of potassium chloride, 10 mEq/L of potassium chloride, or no potassium. A hospital pharmacy can also prepare custom-made solutions with different concentrations of sodium or potassium. In addition, other electrolytes, such as calcium, magnesium, phosphate, acetate, and bicarbonate, can be added to intravenous solutions. Custom-made solutions take time to prepare and are much more expensive than commercial solutions. The use of custom-made solutions is necessary only for patients who have underlying disorders that cause significant electrolyte imbalances.

The use of commercial solutions saves time and expense.

A normal plasma osmolality is 285-295 mOsm/kg. Infusing an intravenous solution peripherally with a much lower osmolality can cause water to move into red blood cells, leading to hemolysis. Thus, intravenous fluids are generally designed to have an osmolality that is either close to 285 or greater (fluids with moderately higher osmolality do not cause problems). Thus, 0.2NS (osmolality = 68) should not be
administered peripherally, but D5 0.2NS (osmolality = 346) or D5 1/2 NS + 20 mEq/L KCl (osmolality = 472) can be administered.

There is controversy about the appropriate sodium content of maintenance fluids, considering the observation that hypotonic fluids may cause hyponatremia, which may have serious sequelae. Hypotonic fluids seem more physiologic given the low sodium content of breast milk and formula. However, hospitalized children often have impaired water excretion, either as a result of volume depletion or of nonosmotic stimuli for antidiuretic hormone (ADH) production (respiratory disease, central nervous system disease, stress, pain, nausea, medications such as narcotics). Hypotonic fluids increase the risk of hyponatremia; 0.2NS is no longer recommended as a standard maintenance fluid and its use is restricted at many hospitals.

**GLUCOSE**

Maintenance fluids usually contain D5, which provides 17 calories/100 mL and nearly 20% of the daily caloric needs. This level is enough to prevent ketone production and helps minimize protein degradation, but the child will lose weight on this regimen. The weight loss is the principal reason why a patient needs to be started on TPN after a few days of maintenance fluids if enteral feedings are still not possible. Maintenance fluids are also lacking in such crucial nutrients as protein, fat, vitamins, and minerals.

**SELECTION OF MAINTENANCE FLUIDS**

D5 1/2 NS + 20 mEq/L KCl is recommended in the child who is NPO and does not have volume depletion or risk factors for nonosmotic ADH production. Children with volume depletion, baseline hyponatremia, or at risk for nonosmotic ADH production (lung infections such as bronchiolitis or pneumonia; central nervous system infection) should receive D5 NS + 20 mEq/L KCl. Surgical patients typically receive isotonic fluids (NS, LR) during surgery and in the recovery room for 6-8 hr postoperatively; the rate is typically approximately two-thirds of the calculated maintenance rate, with dextrose added if clinically indicated. Subsequent maintenance fluids should be D5 NS or LR, with addition of 10-20 mEq/L of KCl based on the serum potassium and the clinical setting. Electrolytes should be measured at least daily in all children receiving more than 50% of maintenance fluids intravenously unless the child is receiving prolonged intravenous fluids (TPN).

These guidelines assume that there is no disease process present that would require an adjustment in either the volume or the electrolyte composition of maintenance fluids. Neonates, and especially premature infants, are outside of the scope of these guidelines given their unique physiology. Children with renal insufficiency may be hyperkalemic or unable to excrete potassium and may not tolerate 10 or 20 mEq/L of potassium. Patients with persistent ADH production because of an underlying disease process (syndrome of inappropriate ADH secretion, congestive heart failure, nephrotic syndrome, liver disease) should receive less than maintenance fluids. Children with meningitis are fluid restricted unless intravascular volume depletion is present (see Chapter 603.1). Treatment is individualized, and careful monitoring is critical.

In children with complicated pathophysiologic derangements, it may be necessary to empirically adjust the electrolyte composition and rate of maintenance fluids on the basis of electrolyte measurements and assessment of fluid balance. In all children, it is critical to carefully monitor weight, urine output, and electrolytes to identify overhydration or underhydration, hyponatremia, and other electrolyte disturbances, and to then adjust the rate or composition of the intravenous solution accordingly.

**VARIATIONS IN MAINTENANCE WATER AND ELECTROLYTES**

The calculation of maintenance water is based on standard assumptions regarding water losses. There are patients, however, in whom these assumptions are incorrect. To identify such situations, it is helpful to understand the source and magnitude of normal water losses. Table 56-5 lists the sources of normal water loss.

**Table 56-5 | Sources of Water Loss**

<table>
<thead>
<tr>
<th>SOURCE</th>
<th>CAUSES OF INCREASED WATER NEEDS</th>
<th>CAUSES OF DECREASED WATER NEEDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Radiant warmer</td>
<td>Incubator (premature infant)</td>
</tr>
<tr>
<td>Lungs</td>
<td>Tachypnea</td>
<td>Humidified ventilator</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Diarrhea</td>
<td>—</td>
</tr>
<tr>
<td>Renal</td>
<td>Polyuria</td>
<td>Oliguria/anuria</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Surgical drain</td>
<td>Third spacing</td>
</tr>
</tbody>
</table>

Urine is the most important contributor to normal water loss. Insensible losses represent approximately one-third of total maintenance water (40% in infants and closer to 25% in adolescents and adults). Insensible losses are composed of evaporative losses from the skin and lungs that cannot be quantitated. The evaporative losses from the skin do not include sweat, which would be considered an additional (sensible) source of water loss. Stool normally represents a minor source of water loss.

Maintenance water and electrolyte needs may be increased or decreased, depending on the clinical situation. This may be obvious, in the case of the infant with profuse diarrhea, or subtle, in the case of the patient who has decreased insensible losses while receiving mechanical ventilation. It is helpful to consider the sources of normal water and electrolyte losses and to determine whether any of these sources is being modified in a specific patient. It is then necessary to adjust maintenance water and electrolyte calculations. Table 56-6 lists a variety of clinical situations that modify normal water and electrolyte losses. The skin can be a source of very significant water loss, particularly in neonates, especially premature infants, who are under radiant warmers or are receiving phototherapy. Very-low-birthweight infants can have insensible losses of 100-200 mL/kg/24 hr. Burns can result in massive losses of water and electrolytes, and there are specific guidelines for fluid management in children with burns (see Chapter 75). Sweat losses of water and electrolytes, especially in a warm climate, can also be significant. Children with cystic fibrosis have increased sodium losses from the skin. Some children with pseudohypoaldosteronism also have increased cutaneous salt losses.

Fever increases evaporative losses from the skin. These losses are somewhat predictable, leading to a 10-15% increase in maintenance water needs for each 1°C (1.8°F) increase in temperature above 38°C (100.4°F). These guidelines are for a patient with a persistent fever; a 1 hr fever spike does not cause an appreciable increase in water needs.

Tachypnea or a tracheostomy causes a decrease in insensible losses from the lungs and can even lead to water absorption via the lungs; a ventilated patient has a decrease in maintenance water requirements. It may be difficult to quantify the changes that take place in the individual patient in these situations.
REPLACEMENT FLUIDS

The gastrointestinal (GI) tract is potentially a source of considerable water loss. GI water losses are accompanied by electrolytes and thus may cause disturbances in intravascular volume and electrolyte concentrations. GI losses are often associated with loss of potassium, leading to hypokalemia. Because of the high bicarbonate concentration in stool, children with diarrhea usually have a metabolic acidosis, which may be accentuated if volume depletion causes hypoperfusion and a concurrent lactic acidosis. Emesis or losses from an NG tube can cause a metabolic alkalosis (see Chapter 55).

In the absence of vomiting, diarrhea, or NG drainage, GI losses of water and electrolytes are usually quite small. All GI losses are considered excessive, and the increase in the water requirement is equal to the volume of fluid losses. Because GI water and electrolyte losses can be precisely measured, it is possible to use an appropriate replacement solution.

It is impossible to predict the losses for the next 24 hr; it is better to replace excessive GI losses as they occur. The child should receive an appropriate maintenance fluid that does not consider the GI losses. The losses should then be replaced after they occur, with use of a solution with a similar electrolyte concentration as the GI fluid. The losses are usually replaced every 1-6 hr, depending on the rate of loss, with very rapid losses being replaced more frequently.

Diarrhea is a common cause of fluid loss in children. It can cause dehydration and electrolyte disorders. In the unusual patient with significant diarrhea and a limited ability to take oral fluid, it is important to have a plan for replacing excessive stool losses. The volume of stool should be measured, and an equal volume of replacement solution should be given. Data are available on the average electrolyte composition of diarrhea in children (Table 56-7). With use of this information, it is possible to design an appropriate replacement solution. The solution shown in Table 56-7 replaces stool losses of sodium, potassium, chloride, and bicarbonate. Each 1 mL of stool should be replaced by 1 mL of this solution. The average electrolyte composition of diarrhea is just an average, and there may be considerable variation. It is therefore advisable to consider measuring the electrolyte composition of a patient's diarrhea if the amount is especially excessive or if the patient's serum electrolyte levels are problematic.

Loss of gastric fluid, via either emesis or NG suction, is also likely to cause dehydration, in that most patients with either condition have impaired oral intake of fluids. Electrolyte disturbances, particularly hypokalemia and metabolic alkalosis, are also common. These complications can be avoided by judicious use of a replacement solution. The composition of gastric fluid shown in Table 56-8 is the basis for designing a replacement solution.

Patients with gastric losses frequently have hypokalemia, although the potassium concentration of gastric fluid is relatively low. The associated urinary loss of potassium is an important cause of hypokalemia in this situation (see Chapter 55). These patients may need additional potassium either in their maintenance fluids or in their replacement fluids to compensate for prior or ongoing urinary losses. Restoration of the patient's intravascular volume, by decreasing aldosterone synthesis, lessens the urinary potassium losses.

Urine output is normally the largest cause of water loss. Diseases such as renal failure and syndrome of inappropriate ADH secretion can lead to a decrease in urine volume. The patient with oliguria or anuria has a decreased need for water and electrolytes; continuation of maintenance fluids produces fluid overload. In contrast, postobstructive diuresis, the polyuric phase of acute tubular necrosis, diabetes mellitus, and diabetes insipidus increase urine production. To prevent dehydration, the patient must receive more than standard maintenance fluids when urine output is excessive. The electrolyte losses in patients with polyuria are variable. In diabetes insipidus, the urine electrolyte concentration is usually low, whereas children with diseases such as juvenile nephronophthisis and obstructive uropathy usually have increased losses of both water and sodium.

The approach to decreased or increased urine output is similar (Table 56-9). The patient receives fluids at a rate to replace insensible losses. This is accomplished by a rate of fluid administration that is 25-40% of the normal maintenance rate, depending on the patient's age. Replacing insensible losses in the anuric child will theoretically maintain an even fluid balance, with the caveat that 25-40% of the normal maintenance rate is only an estimate of insensible losses. In the individual patient, this rate is adjusted on the basis of monitoring of the patient's weight and volume status. Most children with renal insufficiency receive little or no potassium because the kidney is the principal site of potassium excretion.

For the oliguric child, it is important to add a urine replacement solution to prevent dehydration. This issue is especially important in the patient with acute renal failure, in whom output may increase slowly, potentially leading to volume depletion and worsening of renal failure if the patient remains on only insensible fluids. A replacement solution of D5/2NS is usually appropriate initially, although its composition may have to be adjusted if urine output increases significantly.

Most children with polyuria (except in diabetes mellitus; see Chapter 589) should be started on replacement of insensible fluid plus urine losses. This approach avoids the need to attempt to calculate the volume of urine output that is "normal" so that the patient can be given replacement fluid for the excess. In these patients, urine output is, by definition, excessive, and it is important to measure the sodium and potassium concentrations of the urine to help in formulating the urine replacement solution.

Surgical drains and chest tubes can produce measurable fluid output. These fluid losses should be replaced when they are significant. They can be measured and replaced with an appropriate replacement solution. Third space losses, which manifest as edema and ascites, are due to a shift of fluid from the intravascular space into the interstitial space.

Although these losses cannot be quantitated easily, third space losses can be large and may lead to intravascular volume depletion, despite

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**Table 56-7 | Replacement Fluid for Diarrhea**

<table>
<thead>
<tr>
<th>AVERAGE COMPOSITION OF DIARRHEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium: 55 mEq/L</td>
</tr>
<tr>
<td>Potassium: 25 mEq/L</td>
</tr>
<tr>
<td>Bicarbonate: 15 mEq/L</td>
</tr>
</tbody>
</table>

**APPROACH TO REPLACEMENT OF ONGOING LOSSES**

Solution: D5/2NS + 30 mEq/L sodium bicarbonate + 20 mEq/L KCl

Replace stool mL/mL every 1-6 hr

---

**Table 56-8 | Replacement Fluid for Emesis or Nasogastric Losses**

<table>
<thead>
<tr>
<th>AVERAGE COMPOSITION OF GASTRIC FLUID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium: 60 mEq/L</td>
</tr>
<tr>
<td>Potassium: 10 mEq/L</td>
</tr>
<tr>
<td>Chloride: 90 mEq/L</td>
</tr>
</tbody>
</table>

**APPROACH TO REPLACEMENT OF ONGOING LOSSES**

Solution: normal saline + 10 mEq/L KCl

Replace output mL/mL every 1-6 hr

---

**Table 56-9 | Adjusting Fluid Therapy for Altered Renal Output**

<table>
<thead>
<tr>
<th>OLIGURIA/ANURIA</th>
<th>POLYURIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replacement of insensible fluid losses (25-40% of maintenance) with D5/2NS</td>
<td></td>
</tr>
<tr>
<td>Replace urine output mL/mL with D5/2NS ± KCl</td>
<td></td>
</tr>
<tr>
<td>Replacement of insensible fluid losses (25-40% of maintenance) with D5/2NS ± KCl</td>
<td></td>
</tr>
<tr>
<td>Measure urine electrolytes</td>
<td></td>
</tr>
<tr>
<td>Replace urine output mL/mL with solution based on measured urine electrolytes</td>
<td></td>
</tr>
</tbody>
</table>
the patient’s weight gain. Replacement of third space fluid is empirical but should be anticipated in patients who are at risk, such as children who have burns or abdominal surgery. Third space losses and chest tube output are isotonic; thus, they usually require replacement with an isotonic fluid, such as NS or LR. Adjustments in the amount of replacement fluid for third space losses are based on continuing assessment of the patient’s intravascular volume status. Protein losses from chest tube drainage can be significant, occasionally necessitating that 5% albumin be used as a replacement solution.

Bibliography is available at Expert Consult.
Bibliography

Dehydration, most often caused by gastroenteritis, is a common problem in children. Most cases can be managed with oral rehydration (see Chapter 340). Even children with mild to moderate hypotonic or hypernatremic dehydration can be managed with oral rehydration.

**CLINICAL MANIFESTATIONS**

The first step in caring for the child with dehydration is to assess the degree of dehydration (Table 57-1), which dictates both the urgency of the situation and the volume of fluid needed for rehydration. The infant with mild dehydration (3-5% of body weight dehydrated) has few clinical signs or symptoms. The infant may be thirsty; the alert parent may notice a decline in urine output. The history is most helpful. The infant with moderate dehydration has clear physical signs and symptoms. Intravascular space depletion is evident from an increased heart rate and reduced urine output. This patient needs fairly prompt intervention. The infant with severe dehydration is gravely ill. The decrease in intravascular volume may cause rapid heart rate and reduced urine output. The history is most helpful. The infant with severe dehydration should initially receive intravenous therapy. For older children and adults, mild, moderate, or severe dehydration represents a lower percentage of body weight lost. This difference occurs because water accounts for a higher percentage of body weight in infants (see Chapter 55). Clinical assessment of dehydration is only an estimate; thus, the patient must be continually reevaluated during therapy. The degree of dehydration is underestimated in hypernatremic dehydration because the movement of water from the intracellular space to the extracellular space helps preserve the intravascular volume.

**Table 57-1 Clinical Evaluation of Dehydration**

<table>
<thead>
<tr>
<th>Degree of Dehydration</th>
<th>Physical Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild dehydration (&lt;5% in an infant; &lt;3% in an older child or adult)</td>
<td>Normal or increased pulse; decreased urine output; thirsty; normal physical findings</td>
</tr>
<tr>
<td>Moderate dehydration (5-10% in an infant; 3-6% in an older child or adult)</td>
<td>Tachycardia; little or no urine output; irritable/lethargic; sunken eyes and fontanel; decreased tears; dry mucous membranes; mild delay in elasticity (skin turgor); delayed capillary refill (&gt;1.5 sec); cool and pale</td>
</tr>
<tr>
<td>Severe dehydration (&gt;10% in an infant; &gt;6% in an older child or adult)</td>
<td>Peripheral pulses either rapid and weak or absent; decreased blood pressure; no urine output; very sunken eyes and fontanel; no tears; parched mucous membranes; delayed elasticity (poor skin turgor); very delayed capillary refill (&gt;3 sec); cold and mottled; limp; depressed consciousness</td>
</tr>
</tbody>
</table>

The history usually suggests the etiology of the dehydration and may predict whether the patient will have a normal sodium concentration (isotonic dehydration), hypotonic dehydration, or hypernatremic dehydration. The neonate with dehydration due to poor intake of breast milk often has hypernatremic dehydration. Hypernatremic dehydration is likely in any child with losses of hypotonic fluid and poor water intake, such as may occur with diarrhea, and poor oral intake because of anorexia or emesis. Hypotonic dehydration occurs in the child with diarrhea who is taking in large quantities of low-salt fluid, such as water or formula.

Some children with dehydration are appropriately thirsty, but in others the lack of intake is part of the pathophysiology of the dehydration. Even though decreased urine output is present in most children with dehydration, good urine output may be deceivingly absent if a child has an underlying renal defect, such as diabetes insipidus or a salt-wasting nephropathy, or in infants with hypernatremic dehydration.

Physical examination findings are usually proportional to the degree of dehydration. Parents may be helpful in assessment of the child for the presence of sunken eyes, because this finding may be subtle. Pinching and gently twisting the skin of the abdominal or thoracic wall detects tenting of the skin (turgor, elasticity). Tented skin remains in a pinched position rather than springing quickly back to normal. It is difficult to properly assess tenting of the skin in premature infants or severely malnourished children. Activation of the sympathetic nervous system causes tachycardia in children with intravascular volume depletion; diaphoresis may also be present. Postural changes in blood pressure are often helpful for evaluating and assessing the response to therapy in children with dehydration. Tachypnea in children with dehydration may be present secondary to a metabolic acidosis from stool losses of bicarbonate or due to lactic acidosis from shock (see Chapter 70).

**LABORATORY FINDINGS**

Several laboratory findings are useful for evaluating the child with dehydration. The serum sodium concentration determines the type of dehydration. Metabolic acidosis may be a result of stool bicarbonate losses in children with diarrhea, secondary renal insufficiency, or lactic acidosis from shock. The anion gap is useful for differentiating among the various causes of a metabolic acidosis (see Chapter 55). Emesis or nasogastric losses usually cause a metabolic alkalosis. The serum potassium concentration may be low as a result of diarrheal losses. In children with dehydration as a result of emesis, gastric potassium losses, metabolic alkalosis, and urinary potassium losses all contribute to hypokalemia. Metabolic acidosis, which causes a shift of potassium out of cells, and renal insufficiency may lead to hyperkalemia. A combination of mechanisms may be present; thus, it may be difficult to predict the child's acid–base status or serum potassium level from the history alone.

The blood urea nitrogen (BUN) value and serum creatinine concentration are useful in assessing the child with dehydration. Volume depletion without parenchymal renal injury may cause a disproportionate increase in the BUN with little or no change in the creatinine concentration. This condition is secondary to increased passive resorption of urea in the proximal tubule as a result of appropriate renal conservation of sodium and water. The increase in the BUN with moderate or severe dehydration may be absent or blunted in the child with poor protein intake, because urea production depends on protein degradation. The BUN may be disproportionately increased in the child with increased urea production, as occurs with a gastrointestinal bleed or with the use of glucocorticoids, which increase catabolism. A significant elevation of the creatinine concentration suggests renal insufficiency, although a small, transient increase can occur with dehydration. Acute tubular necrosis (acute kidney injury) (see Chapter 535) because of volume depletion is the most common etiology of renal insufficiency in a child with volume depletion, but occasionally the child may have previously undetected chronic renal insufficiency or an alternative explanation for the acute renal failure. Renal vein thrombosis is a well-described sequela of severe dehydration in infants;
possible findings include thrombocytopenia and hematuria (see Chapter 519.7).

Hemoconcentration from dehydration causes increases in hematocrit, hemoglobin, and serum proteins. These values normalize with rehydration. A normal hemoglobin concentration during acute dehydration may mask an underlying anemia. A decreased albumin level in a dehydrated patient suggests a chronic disease, such as malnutrition, nephrotic syndrome, or liver disease, or an acute process, such as capillary leak. An acute or chronic protein-losing enteropathy may also cause a low serum albumin concentration.

**CALCULATION OF THE FLUID DEFICIT**

Determining the fluid deficit necessitates clinical determination of the percentage of dehydration and multiplication of this percentage by the patient's weight; a child who weighs 10 kg and is 10% dehydrated has a fluid deficit of 1 L.

**APPROACH TO SEVERE DEHYDRATION**

The child with dehydration needs acute intervention to ensure that there is adequate tissue perfusion. This resuscitation phase requires rapid restoration of the circulating intravascular volume and treatment of shock with an isotonic solution, such as normal saline (NS) or Ringer lactate (LR) (see Chapter 70). The child is given a fluid bolus, usually 20 mL/kg of the isotonic fluid, over approximately 20 min. The child with severe dehydration may require multiple fluid boluses and may need to receive the boluses as fast as possible. In a child with a known or probable metabolic alkalosis (the child with isolated vomiting), LR should not be used because the lactate would worsen the alkalosis.

Colloids, such as blood, 5% albumin, and plasma, are rarely needed for fluid boluses. A crystalloid solution (NS or LR) is satisfactory, with both less infectious risk and lower cost. Blood is obviously indicated in the child with significant anemia or acute blood loss. Plasma is useful for children with a coagulopathy. The child with hypoalbuminemia may benefit from 5% albumin, although there is evidence that albumin infusions increase mortality in adults. The volume and the infusion rate for colloids are generally modified compared with crystalloids (see Chapters 473).

The initial resuscitation and rehydration phase is complete when the child has an adequate intravascular volume. Typically, the child shows clinical improvement, including a lower heart rate, normalization of blood pressure, improved perfusion, better urine output, and a more alert affect.

With adequate intravascular volume, it is appropriate to plan the fluid therapy for the next 24 hr. A general approach is outlined in Table 57-2, with the caveat that there are many different approaches to correcting dehydration. In isonatremic or hyponatremic dehydration, the entire fluid deficit is corrected over 24 hr; a slower approach is used for hypernatremic dehydration (discussed later). The volume of isotonic fluids that the patient has received is subtracted from this total. The remaining fluid volume is then administered over 24 hr. The potassium concentration may need to be decreased or, less commonly, increased, depending on the clinical situation. Potassium is not usually included in the intravenous fluids until the patient voids and normal renal function is documented via measurement of BUN and creatinine. Children with significant ongoing losses need to receive an appropriate replacement solution (see Chapter 56).

**MONITORING AND ADJUSTING THERAPY**

The formulation of a plan for correcting a child's dehydration is only the beginning of management. All calculations in fluid therapy are only approximations. This statement is especially true for the assessment of percentage dehydration. It is equally important to monitor the patient during treatment and to modify therapy on the basis of the clinical situation. Table 57-3 lists the cornerstones of patient monitoring. The patient's vital signs are useful indicators of intravascular volume status. The child with decreased blood pressure and an increased heart rate will probably benefit from a fluid bolus. Central venous pressure is an excellent indicator of fluid status in the critically ill child with shock.

The patient's intake and output are critically important in the dehydrated child. The child who, after 8 hr of therapy, has more output than input because of continuing diarrhea needs to be started on a replacement solution. See the guidelines in Chapter 56 for selecting an appropriate replacement solution. Urine output is useful for evaluating the success of therapy. Good urine output indicates that rehydration has been successful.

Signs of dehydration on physical examination suggest the need for continued rehydration. Signs of fluid overload, such as edema and pulmonary congestion, are present in the child who is overhydrated. An accurate daily weight measurement is critical for the management of the dehydrated child. There should be a gain in weight during successful therapy.

Measurement of serum electrolyte levels at least daily is appropriate for any child who is receiving intravenous rehydration. Such a child is at risk for sodium, potassium, and acid–base disorders. It is always important to look at trends. For instance, a sodium value of 144 mEq/L is normal; but if the sodium concentration was 136 mEq/L 12 hr earlier, then there is a distinct risk that the child will be hypernatremic in 12 or 24 hr. It is advisable to be proactive in adjusting fluid therapy.

Both hypokalemia and hyperkalemia are potentially serious (see Chapter 55). Because dehydration can be associated with acute renal failure and hyperkalemia, potassium is withheld from intravenous fluids until the patient has voided. The potassium concentration in the patient's intravenous fluids is not rigidly prescribed. Rather, the patient's serum potassium level and underlying renal function are used to modify potassium delivery. The patient with an elevated creatinine value and a potassium level of 5 mEq/L does not receive any potassium until the serum potassium level decreases. Conversely, the patient with a potassium level of 2.5 mEq/L may require additional potassium.

Metabolic acidosis can be quite severe in dehydrated children. Although normal kidneys eventually correct this problem, a child with renal dysfunction may be unable to correct a metabolic acidosis, and a portion of the patient's intravenous sodium chloride may have to be replaced with sodium bicarbonate or sodium acetate.

The serum potassium level is modified by the patient's acid–base status. Acidosis increases serum potassium by causing intracellular potassium to move into the extracellular space. Thus, as acidosis is corrected, the potassium concentration decreases. Again, it is best to anticipate this problem and to monitor the serum potassium concentration and adjust potassium administration appropriately.
HYPONATREMIC DEHYDRATION
The pathogenesis of hyponatremic dehydration usually involves a combination of sodium and water loss and water retention to compensate for the volume depletion. The patient has a pathologic increase in fluid loss, and the lost fluid contains sodium. Most fluid that is lost has a lower sodium concentration, so patients with only fluid loss would have hyponatremia. Diarrhea has, on average, a sodium concentration of 50 mEq/L. Replacing diarrheal fluid with water, which has almost no sodium, causes a reduction in the serum sodium concentration. The volume depletion stimulates synthesis of antidiuretic hormone, resulting in reduced renal water excretion. Hence, the body’s usual mechanism for preventing hyponatremia, renal water excretion, is blocked. The risk of hyponatremia is further increased if the volume depletion is a result of loss of fluid with a higher sodium concentration, as may occur with renal salt wasting, third space losses, or diarrhea with high sodium content (cholera).

The initial goal in treating hyponatremia is correction of intravascular volume depletion with isotonic fluid (NS or LR). An overly rapid (>12 mEq/L over the first 24 hr) or overcorrection in the serum sodium concentration (>135 mEq/L) is associated with an increased risk of central pontine myelinolysis (see Chapter 55). Most patients with hyponatremic dehydration do well with the same basic strategy that is outlined in Table 57-2. Again, potassium delivery is adjusted according to the initial serum potassium level and the patient’s renal function. Potassium is not given until the patient voids.

The patient’s sodium concentration is monitored closely to ensure appropriate correction, and the sodium concentration of the fluid is adjusted accordingly. Patients with ongoing losses require an appropriate replacement solution (see Chapter 56). Patients with neurologic symptoms (seizures) as a result of hyponatremia need to receive an acute infusion of hypertonic (3%) saline to increase the serum sodium concentration rapidly (see Chapter 55).

HYPERNATREMIC DEHYDRATION
Hyponatremic dehydration is the most dangerous form of dehydration because of complications of hypernatremia and of therapy. Hypernatremia can cause serious neurologic damage, including central nervous system hemorrhages and thrombosis. This damage appears to be secondary to the movement of water from the brain cells into the hypertonic extracellular fluid, causing brain cell shrinkage and tearing blood vessels within the brain (see Chapter 55).

The movement of water from the intracellular space to the extracellular space during hypernatremic dehydration partially protects the intravascular volume. Unfortunately, because the initial manifestations are milder, children with hypernatremic dehydration are often brought for medical attention with more profound dehydration.

Children with hypernatremic dehydration are often lethargic, and they may be irritable when touched. Hyponatremia may cause fever, hypotension, and hyperreflexia. More severe neurologic symptoms may develop if cerebral bleeding or thrombosis occurs.

Overly rapid treatment of hypernatremic dehydration may cause significant morbidity and mortality. Idiogenic osmoles are generated within the brain during the development of hypernatremia. These idiogenic osmoles increase the osmolality within the cells of the brain, providing protection against brain cell shrinkage caused by movement of water out of the cells and into the hypertonic extracellular fluid. They dissipate slowly during the correction of hypernatremia. With overly rapid lowering of the extracellular osmolality during the correction of hypernatremia, an osmotic gradient may be created that causes water movement from the extracellular space into the cells of the brain, producing cerebral edema. Symptoms of the resultant cerebral edema can range from seizures to brain herniation and death.

To minimize the risk of cerebral edema during the correction of hypernatremic dehydration, the serum sodium concentration should not decrease by >12 mEq/L every 24 hr. The deficits in severe hypernatremic dehydration may need to be corrected over 2-4 days (Table 57-4).

The initial resuscitation of hypernatremic dehydration requires restoration of the intravascular volume with NS. LR should not be used because it is more hypotonic than NS and may cause too rapid a decrease in the serum sodium concentration, especially if multiple fluid boluses are necessary.

To avoid cerebral edema during correction of hypernatremic dehydration, the fluid deficit is corrected slowly. The rate of correction depends on the initial sodium concentration (see Table 57-4). There is no general agreement on the choice or the rate of fluid for correcting hypernatremic dehydration. The choice and the rate of fluid administration are not nearly as important as vigilant monitoring of the serum sodium concentration and adjustment of the therapy according to the result (see Table 57-4). The rate of decrease of the serum sodium concentration is roughly related to the “free water” delivery, although there is considerable variation between patients. Free water is water without sodium. NS contains no free water, half-NS (½NS) is 50% free water, and water is 100% free water. Smaller patients, to achieve the same decrease in the sodium concentration, tend to need higher amounts of free water delivery per kilogram because of higher insensible fluid losses. Five percent dextrose (D5) with ½NS is usually an appropriate starting solution for a patient with hypernatremic dehydration. Some patients, especially infants with ongoing high insensible water losses, may need to receive D5 2N or NS, which should be used with great caution and constant monitoring. Others require D5 0.5 NS. A child with dehydration as a result of pure free water loss, as usually occurs with diabetes insipidus, usually needs a more hypotonic fluid than a child with depletion of both sodium and water due to diarrhea.

Adjustment in the sodium concentration of the intravenous fluid is the most common approach to modifying the rate of decrease in the serum concentration (see Table 57-4). For difficult-to-manage patients with severe hypernatremia, having 2 intravenous solutions (e.g., D5 ½ NS and D5 NS, both with the same concentration of potassium) at the bedside can facilitate this approach by allowing for rapid adjustments of the rates of the 2 fluids. If the serum sodium concentration decreases too rapidly, the rate of D5 NS can be increased and the rate of D5 ½ NS can be decreased by the same amount. Adjustment in the total rate of fluid delivery is another approach to modifying free water delivery. For example, if the serum sodium concentration is decreasing too slowly, the rate of the intravenous fluid can be increased, thereby increasing the delivery of free water. There is limited flexibility in modifying the rate of the intravenous fluid because patients generally should receive 1.25-1.5 times the normal maintenance fluid rate. Nevertheless, in some situations, it can be a helpful adjustment.

Because increasing the rate of the intravenous fluid increases the rate of decline of the sodium concentration, signs of volume depletion are

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**Table 57-4** Treatment of Hypernatremic Dehydration

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Volume Depletion</th>
<th>Sodium Concentration</th>
<th>Sodium Decrease</th>
<th>Rate of Correction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal saline (NS)</td>
<td>20 mL/kg</td>
<td>145-157 mEq/L</td>
<td>Too rapidly</td>
<td>1.25-1.5 times</td>
</tr>
<tr>
<td>Sodium decreases</td>
<td></td>
<td>158-170 mEq/L</td>
<td>Too rapidly</td>
<td>1.25-1.5 times</td>
</tr>
<tr>
<td>Sodium decreases</td>
<td></td>
<td>171-183 mEq/L</td>
<td>Too rapidly</td>
<td>1.25-1.5 times</td>
</tr>
<tr>
<td>Sodium decreases</td>
<td></td>
<td>184-196 mEq/L</td>
<td>Too rapidly</td>
<td>1.25-1.5 times</td>
</tr>
</tbody>
</table>

**Follow-up actions:**
- Adjust fluid on basis of clinical status and serum sodium concentration.
- Signs of volume depletion: administer normal saline (20 mL/kg).
- Sodium decreases too rapidly: increase sodium concentration of intravenous fluid.
- Sodium decreases too slowly: decrease sodium concentration of intravenous fluid.
- Increase rate of intravenous fluid.
- Replace ongoing losses as they occur.
treated with additional isotonic fluid boluses. The serum potassium concentration and the level of renal function dictate the potassium concentration of the intravenous fluid; potassium is withheld until the patient voids. Patients with hypernatremic dehydration need an appropriate replacement solution if they have ongoing, excessive losses (see Chapter 56).

Seizures are the most common manifestation of cerebral edema from an overly rapid decrease of the serum sodium concentration during correction of hypernatremic dehydration. Signs of increased intracranial pressure or impending herniation may develop quite rapidly (see Chapter 68). Acutely, increasing the serum concentration via an infusion of 3% sodium chloride can reverse the cerebral edema. Each 1 mL/kg of 3% sodium chloride increases the serum sodium concentration by approximately 1 mEq/L. An infusion of 4 mL/kg often results in resolution of the symptoms. This strategy is similar to that used for treating symptomatic hyponatremia (see Chapter 55).

In patients with severe hypernatremia, oral fluids must be used cautiously. Infant formula, because of its low sodium concentration, has a high free water content, and especially if added to intravenous therapy, it may contribute to a rapid decrease in the serum sodium concentration. Less hypotonic fluid, such as an oral rehydration solution, may be more appropriate initially (see Chapter 340). If oral intake is allowed, its contribution to free water delivery must be taken into account, and adjustment in the intravenous fluid is usually appropriate. Judicious monitoring of the serum sodium concentration is critical.

Bibliography is available at Expert Consult.
Bibliography
ACUTE DIARRHEA
See Chapter 340.

PYLORIC STENOSIS
See Chapter 329.1.

PERIOPERATIVE FLUIDS
See Chapter 61.
The role of genetic factors in drug disposition and response, pharmacogenetics, has resulted in many examples of how variations in human genes can lead to interindividual differences in pharmacokinetics and drug response at the level of individual patients. Pharmacogenetic variability contributes to the broad range of drug responses observed in children at any given age or developmental stage; it is expected that children will benefit from the promise of personalized medicine—identifying the right drug for the right patient at the right time (Fig. 59-1). Numerous maturational processes occur from birth through adolescence such that utilization of information resulting from the Human Gene Project and related initiatives must take into account the changing patterns of gene expression that occur over development to improve pharmacotherapeutics in children.

**PHARMACOGENETICS, PHARMACOGENOMICS, AND THE CONCEPT OF PERSONALIZED MEDICINE**

The terms pharmacogenomics and pharmacogenetics tend to be used interchangeably, and precise, consensus definitions are often difficult to determine. Pharmacogenetics classically is defined as the study or clinical testing of genetic variations that give rise to interindividual differences in the response to drugs. The earliest examples of pharmacogenetic traits include specific adverse drug reactions, such as unusually prolonged respiratory muscle paralysis caused by succinylcholine, hemolysis associated with antimalarial therapy, and isoniazid-induced neurotoxicity, all of which are a consequence of inherited variations in enzyme activity. The importance of pharmacogenetic differences has become better understood and is exemplified by the fact that the half-lives of several drugs are more similar in monozygotic twins than in dizygotic twins. However, it is important to note that in addition to pharmacogenetic differences, environmental factors (diet, smoking status, concomitant drug or toxicant exposure), physiologic variables (age, sex, disease, pregnancy), and patient compliance all contribute to variations in drug metabolism and response. Likewise, ethnicity is another potential genetic determinant of drug variability. For example, Chinese patients who are HLA-B*1502-positive and white patients who are positive for HLA-A*3101 have an increased risk of carbamazepine-induced Stevens-Johnson syndrome; white patients who are HLA-B*5701-positive have an increased risk of hypersensitivity to abacavir (Table 59-1).

**Pharmacogenomics** represents the marriage of pharmacology and genomics, and can be defined as the broader application of genome-wide technologies and strategies to identify both disease processes that represent new targets for drug development and factors predictive of efficacy and risk of adverse drug reactions.

**Pharmacokinetics** describes temporal aspects of what the body does to a drug. It is often studied in conjunction with pharmacodynamics, which explores what a drug does to the body (see Chapter 60). The pharmacokinetic properties of a drug are determined by the genes that control the drug's disposition in the body (absorption, distribution, metabolism, excretion). Drug metabolizing enzymes and drug transporters play a particularly important role in this process (Table 59-2), and the functional consequences of genetic variations in many drug metabolizing enzymes have been described between subjects of both similar and different ethnic groups. The most common clinical manifestation of pharmacogenetic variability in drug biotransformation is an increased risk of concentration-dependent toxicity as a result of reduced clearance and consequent drug accumulation. On the other hand, rapid metabolism can lead to accumulation of a toxic metabolite, as has been reported for the hepatic conversion of codeine to morphine in 4 children ages 2-5 yr who received codeine for pain after tonsillectomy and adenoidectomy. This variant pharmacokinetics resulted in 3 deaths and 1 near-death from respiratory depression. As a result of these concerns, physicians are reminded to prescribe any drug at the lowest effective dose, for the shortest time, and only on an as-needed basis.

An equally important manifestation of this variability is lack of efficacy resulting from variations in metabolism of prodrugs. The pharmacogenetics of drug receptors and other target proteins involved in signal transduction or disease pathogenesis can also be expected to contribute significantly to interindividual variability in drug disposition and response.

**Therapeutic drug monitoring** programs recognize that all patients are unique and that the serum concentration-time data for an individual patient theoretically can be used to optimize pharmacotherapy. These programs have been the earliest application of personalized medicine; however, routine therapeutic drug monitoring does not necessarily translate to improved patient outcome in all situations.

The concept of personalized medicine is based on the premise that the wealth of information accompanying the application of genomic technologies to patient-related problems will allow for (1) stratification of patient populations according to their response to a particular medication (e.g., lack of drug efficacy or excessive toxicity), and (2) stratification of diseases into specific subtypes that are categorized according to genomic criteria and by response to particular treatments.

**DEFINITION OF PHARMACOGENETIC TERMS**

Genetic polymorphisms (variations) result when copies of a specific gene present within a population do not have identical nucleotide sequences. The term **allele** refers to one of a series of alternative DNA sequences for a particular gene. In humans, there are 2 copies of every gene. An individual's genotype for a given gene is determined by the set of alleles that the individual possesses. The most common form of genetic variation involves a single base change at a given location, referred to as a **single-nucleotide polymorphism (SNP)** (see Chapter 81). At the other end of the spectrum are **copy number variations**, which refer to the deletion or duplication of identical or near identical DNA sequences that may be thousands to millions of bases in size. Copy number variations occur less frequently than SNPs, but may constitute 0.5-1% of an individual's genome, and thereby contribute significantly to phenotypic variation. **Haplotypes** are collections of SNPs and other allelic variations that are located close to one another and when inherited together these create a catalog of haplotypes, or **HapMap**. When the alleles at a particular gene locus on both chromosomes are identical, a **homozygous** state exists, whereas the term **heterozygous** refers to the situation in which different alleles are present at the same gene locus. The term **genotype** refers to an individual's
Our current understanding of pharmacogenetic principles involves enzymes responsible for drug biotransformation. Individuals are classified as being “fast,” “rapid,” or “extensive” metabolizers at one end of the spectrum, and “slow” or “poor” metabolizers at the other end of the continuum. This may or may not also include an “intermediate” metabolizer group, depending on the particular enzyme. With regard to biotransformation, children are more complex than adults as fetuses differ from that observed in adults (e.g., developmental stages at which functional activity is acquired after birth). Furthermore, there may be discrete periods during childhood in which the genotype-phenotype relationship may differ from that observed in adults (e.g., developmental stages at which enzyme activity appears to be greater in children than in adults). (Adapted from Leeder JS: Translating pharmacogenetics and pharmacogenomics into drug development for clinical pediatric and beyond. Drug Discov Today 9:567–573, 2004.) and newborns may be phenotypically “slow” or “poor” metabolizers for certain drug-metabolizing pathways because of their stage of development, and may acquire a phenotype consistent with their genotype at some point later in the developmental process as they mature. Examples of drug-metabolizing pathways that are significantly affected by ontogeny include glucuronidation and some of the cytochrome P450 (CYP) activities (see Chapters 60, 96, and 97). It is also apparent that not all infants acquire drug metabolism activity at the same rate. This is attributable to interactions between genetics and environmental factors. Interindividual variability in the trajectory (i.e., rate and extent) of acquired drug biotransformation capacity may be considered a developmental phenotype (Fig. 59–2), and it helps to explain the considerable variability in some CYP activities observed immediately after birth.

**Pharmacogenetic, Pharmacogenomic, and Pharmacoproteomic Tools**

Several genotyping platforms are approved by the Food and Drug Administration and are beginning to enter the clinical arena. The Roche AmpliChip CYP450 Test was the first such device to receive FDA.
approval, and many additional products have become available (https://www.pharmgkb.org/views/viewGeneticTests.action). In general, applications are limited to 1 or 2 genes, such as CYP2C9 and VKORC1 genotyping to guide warfarin therapy or genotyping of UGT1A1 to reduce the risk of irinotecan toxicity. A more comprehensive chip that covers >90% of the absorption, distribution, metabolism, and excretion markers as defined by the PharmaADME group (http://pharmaadme.org) is available for drug development and research purposes, and the National Institute of General Medical Sciences–sponsored Pharmacogenomics Research Network has developed a list of high-priority genes of interest (http://pgrn.org/download/attachments/131165/PGRN-seq%20Gene%20List%2010-15-12%20Scherer%20Genes.pdf?version=1&modificationDate=1350681059000&api=2).

In contrast to pharmacogenetic studies that typically target single genes, pharmacogenomic analyses are considerably broader in scope and focus on complex and highly variable drug-related phenotypes with targeting of many genes. Genomewide genotyping technologies have progressed beyond "SNP chips" to evaluate genetic variation at more than 1 million sites throughout an individual genome for SNP and copy number variation analyses to include massively parallel “next-generation sequencing” technologies. Genomewide association studies have been conducted in several pediatric settings, acute lymphoblastic leukemia, and pediatric inflammatory bowel disease. One goal of this type of study is to identify novel genes involved in disease pathogenesis that can lead to new therapeutic targets. Genomewide association studies are also being applied to identify genetic associations with response to drugs, such as warfarin and clopidogrel, and risk for drug-induced toxicity, including statin-induced myopathy and flucloxacinil hepatotoxicity. The "Manhattan plot," a form of data presentation for genomewide association studies, is common in many medical journals (Fig. 59-3A). Next-generation sequencing is being applied to rapidly diagnose mendelian disorders and pathologies thought to have a genetic origin when all other diagnostic approaches have been exhausted.

Investigating differential gene expression before and after drug exposure has the potential to correlate gene expression with variable drug responses and possibly uncover the mechanisms of tissue-specific drug toxicities. These types of studies use microarray technology or RNA-Seq (based on next-generation sequencing technologies) to monitor global changes in expression of thousands of genes (the transcriptome) simultaneously. The underlying hypothesis of these global

### Table 59-1 Examples of Effects of Gene Polymorphisms on Drug Response

<table>
<thead>
<tr>
<th>GENE</th>
<th>ENZYME/TARGET</th>
<th>DRUG</th>
<th>CLINICAL RESPONSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCHE</td>
<td>Butyrylcholinesterase</td>
<td>Succinylcholine</td>
<td>Prolonged paralysis</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Cytochrome P450 2C9</td>
<td>Warfarin</td>
<td>Individuals having one or more reduced function alleles require lower doses of warfarin for optimal anticoagulation, especially initial anticoagulant control</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Cytochrome P450 2C19</td>
<td>Clopidogrel</td>
<td>Individuals having one or more loss-of-function alleles have reduced capacity to form the pharmacologically active metabolite of clopidogrel and reduced antiplatelet effect</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Cytochrome P450 2D6</td>
<td>Codeine</td>
<td>Poor metabolizers—individuals with 2 loss-of-function alleles—do not metabolize codeine to morphine and thus experience no analgesic effect; ultrarapid metabolizers (3 or more functional alleles) may experience morphine toxicity</td>
</tr>
<tr>
<td>G6PD</td>
<td>Glucose-6-phosphate dehydrogenase</td>
<td>Primaquine (others)</td>
<td>Hemolysis</td>
</tr>
<tr>
<td>HLA-A*3101</td>
<td>Human leukocyte antigen A31</td>
<td>Carbamazepine</td>
<td>Carriers of the HLA-A*3101 allele have an increased risk of Stevens-Johnson syndrome and toxic epidermal necrosis from carbamazepine</td>
</tr>
<tr>
<td>HLA-B*1502</td>
<td>Human leukocyte antigen B15</td>
<td>Allopurinol</td>
<td>Han Chinese carriers of the HLA-B*1502 allele have an increased risk of Stevens-Johnson syndrome and toxic epidermal necrosis from carbamazepine</td>
</tr>
<tr>
<td>HLA-B*5701</td>
<td>Human leukocyte antigen B57</td>
<td>Abacavir</td>
<td>Carriers of the HLA-B*5701 allele have an increased risk of hypersensitivity reactions to abacavir and abacavir- and flucloxacinil-induced liver injury</td>
</tr>
<tr>
<td>HLA-B*5801</td>
<td>Human leukocyte antigen B58</td>
<td>Allopurinol</td>
<td>Carriers of the HLA-B*5801 allele have an increased risk of severe cutaneous adverse reactions to allopurinol, including hypersensitivity reactions, Stevens-Johnson syndrome, and toxic epidermal necrosis</td>
</tr>
<tr>
<td>NAT2</td>
<td>N-acetyltransferase 2</td>
<td>Isoniazid, hydralazine</td>
<td>Individuals homozygous for “slow acetylation” polymorphisms are more susceptible to isoniazid toxicity, or hydralazine-induced systemic lupus erythematosus</td>
</tr>
<tr>
<td>SLCO1B1</td>
<td>Organic anion transporting protein (OATP) 1B1</td>
<td>Simvastatin</td>
<td>Carriers of the SLCO1B1*5 allele are at increased risk for musculoskeletal side effects from simvastatin</td>
</tr>
<tr>
<td>TPMT</td>
<td>Thiopurine S-methyltransferase</td>
<td>Azathioprine 6-Mercaptopurine</td>
<td>Individuals homozygous for an inactivating mutation have severe toxicity if treated with standard doses of azathioprine or 6-mercaptopurine; rapid metabolism causes undertreatment</td>
</tr>
<tr>
<td>UGT1A1</td>
<td>Uridine diphosphoglucuronosyltransferase 1A1</td>
<td>Irinotecan</td>
<td>The UGT1A1*28 allele is associated with decreased glucuronidation of SN-38, the active metabolite of irinotecan, and increased risk of neutropenia</td>
</tr>
<tr>
<td>VKORC1</td>
<td>Vitamin K oxidoreductase complex 1</td>
<td>Warfarin</td>
<td>Individuals with a haplotype associated with reduced expression of the VKORC1 protein, the therapeutic target of warfarin, require lower doses of the drug for stable anticoagulation</td>
</tr>
</tbody>
</table>
gene profiling studies is that the measured signal intensity for each
gene transcript represents its relative expression level. RNA-Seq allows
absolute quantitation of gene expression, as well as detection of alterna-
tive splicing events. Gene expression profiling data are used to improve
disease classification and risk stratification, and are utilized commonly
in oncology. This approach was used to address treatment resistance
in acute lymphoblastic leukemia, and has provided clinically relevant
insights into the mechanistic basis of drug resistance and the genomic
basis of interindividual variability in drug response. Subsets of tran-
scripts, or gene expression “signatures,” are being investigated as poten-
tial prognostic indicators for identifying patients at risk for treatment
failure (Fig. 59-3).

Proteomic studies use many different techniques to detect, quantify,
and identify proteins in a sample (expression proteomics), and to

Table 59-2 Some Important Relationships Between Drugs and Cytochrome P450 (CYP) Enzymes* and P-Glycoprotein
(P-gp) Transporter

<table>
<thead>
<tr>
<th>ENZYME</th>
<th>DRUG SUBSTRATES</th>
<th>INHIBITORS</th>
<th>INDUCERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Caffeine, clozapine (Anafranil), clozapine (Clozaril), theophylline</td>
<td>Cimetidine (Tagamet), Fluvoxamine (Luvox), Ciprofloxacin (Cipro)</td>
<td>Omeprazole (Prilosec), Tobacco</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Diclofenac (Voltaren), ibuprofen (Motrin), piroxicam (Feldene), losartan (Cozaar), irbesartan (Avapro), celecoxib (Celebrex), tolbutamide (Orinase), warfarin (Coumadin), phenytoin (Dilantin)</td>
<td>Fluconazole (Diflucan), Fluvastatin (Lescol), Amiodarone (Cordarone), Zafirlukast (Accolate)</td>
<td>Rifampin (Rifadin)</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Omeprazole, Lansoprazole (Prevacid), pantoprazole (Protonix), (S)-mephentyno, (S)-citalopram (Lexapro), nelfinavir (Viracept), diazepam (Valium), voriconazole (Vfend)</td>
<td>Cimetidine Fluvoxamine</td>
<td>Rifampin</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>CNS-active agents: Atomoxetine (Strattera), amitriptyline (Elavil), desipramine (Norpramin), imipramine (Tofranil), paroxetine (Paxil), haloperidol (Haldol), risperdone (Risperdal), thioridazine (Mellaril)</td>
<td>Antiarrhythmic agents: Mexiletine (Mexitil), propafenone (Rythmol)</td>
<td>β Blockers: Propranolol (Inderal), metoprolol (Lopressor), timolol (Blocadren)</td>
</tr>
<tr>
<td></td>
<td>Narcotics: Codeine, dextromethorphan, hydrocodone (Vicodin)</td>
<td>Others: Tamoxifen (Nolvadex)</td>
<td></td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Calcium channel blockers: Diltiazem (Cardizem), felodipine (Plendil), nimodipine (Nimotop), nifedipine (Adalat), nisoldipine (Sular), verapamil (Calan)</td>
<td>Immunosuppressive agents: Cyclosporine (Sandimmune, Neoral), tacrolimus (Prograf)</td>
<td>Steroids: Budesonide (Pulmicort), cortisol, 17β-estradiol, progesterone, testosterone</td>
</tr>
<tr>
<td></td>
<td>Macrolide antibiotics: Clarithromycin (Biaxin), erythromycin (Erythromycin), treolandomycin (TACO)</td>
<td>Anticancer agents: Cyclophosphamide (Cytoxan), gefitinib (Iressa), ifosfamide (Ifex), tamoxifen, vincristine (Oncovin), vinblastine (Velban)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Benzodiazepines: Alprazolam (Xanax), midazolam (Versed), triazolam (Halcion)</td>
<td>Opioids: Alfentanil (Alfenta), fentanyl (Sublimaze), sufentanil (Sufenta)</td>
<td>HMG-CoA reductase inhibitors: Lovastatin (Mevacor), simvastatin (Zocor), atorvastatin (Lipitor)</td>
</tr>
<tr>
<td></td>
<td>HIV protease inhibitors: Indinavir (Crixivan), nelfinavir, ritonavir (Norvir), saquinavir (Invirase, Fortovase), amprenavir (Agenerase)</td>
<td>Others: Quinidine (Quinidex), sildenafil (Viagra), elithiptan (Relpax), ziprasidone (Geodon)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P-gp: Aldosterone, amphenir, atorvastatin, cyclosporine, dexamethasone (Decadron), digoxin (Lanoxin), diltiazem, domperidone (Motilium), doxorubicin (Adriamycin), erythromycin, etoposide (VePesid), gefitinb, fexofenadine (Allegra), hydrocortisone, indinavir, ivermectin (Stromectol), lovastatin (Lopandam, (Modium), nelfinav, ondansetron (Zofran), paclitaxel (Taxol), quinidine, saquinavir, simvastatin, verapamil, vinblastine, vincristine</td>
<td>Amiodarone Carvedilol (Coreg) Clarithromycin Cyclosporine Erythromycin Itraconazole Ketoconazole Quinidine Ritonavin Tamoxifen Verapamil</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Amprenavir Clofazimazole (Mycelex), Phenothiazine Ritonavir St. John’s wort</td>
</tr>
</tbody>
</table>

†Also available generically.  
‡Can be both an inhibitor and an inducer.
CNS, central nervous system; HMG-CoA, 3-hydroxy-3-methylglutaryl–coenzyme A.

characterize protein function in terms of activity and protein–protein or protein–nucleic acid interactions (functional proteomics). Two-dimensional electrophoresis coupled with mass spectral detection is the mainstay of expression proteomics. Protein "spots" of interest are "picked," digested with a proteolytic enzyme such as trypsin, and identified by mass spectrometry. The data generated are compared with theoretically derived peptide mass databases for protein identification.

Metabolomics and metabonomics utilize sophisticated analytical platforms, such as nuclear magnetic resonance spectroscopy and liquid or gas chromatography coupled with mass spectral detection, to measure the concentrations of all small molecules present in a sample. Metabolomics refers to the study of the complete set of low-molecular-weight molecules (metabolites) present in a living system (cell, tissue, organ or organism) at a particular developmental or pathological state. Metabonomics is defined as the study of how the metabolic profile of biological systems changes in response to alterations because of physiologic stimuli, toxic exposures, dietary changes, etc. Pharmacometabonomics has been defined as "the prediction of the outcome, efficacy or toxicity, of a drug or xenobiotic intervention in an individual based on a mathematical model of preintervention metabolite signatures." In the future, integrating metabolomics with pharmacogenomics and transcriptomics will result in a more "systems-based" understanding of cellular processes, especially in the context of drug efficacy and toxicity.

DEVELOPMENTAL PHARMACOGENETICS OF DRUG BIOTRANSFORMATION: APPLICATIONS TO PEDIATRIC DRUG THERAPY PRACTICE

The major consequence of pharmacogenetic polymorphisms in drug metabolizing enzymes is concentration-dependent toxicity caused by impaired drug clearance. In certain cases, reduced conversion of prodrug to therapeutically active compounds is also of clinical importance (see Table 59-2). Chemical modification of drugs via biotransformation reactions generally results in termination of biologic activity through decreased affinity for receptors or other cellular targets as well as more rapid elimination from the body. The process of drug biotransformation can be very complex, but is characterized by 3 important features. First is the concept of broad substrate specificity—a single
isozyme may metabolize a large variety of chemically diverse compounds. Second, many different enzymes may be involved in the biotransformation of a single drug (enzyme multiplicity). Finally, a given drug may undergo several different types of reactions. One example of this product multiplicity occurs with racemic warfarin, where at least 7 different hydroxylated metabolites are produced by different CYP isoforms.

**Drug biotransformation** reactions are conveniently classified into 2 main types, phase I and phase II reactions, which occur sequentially and serve to terminate biologic activity and enhance elimination (see Chapter 60). Phase I reactions introduce or reveal (via oxidation, reduction, or hydrolysis) a functional group within the substrate drug molecule that serves as a site for a phase II conjugation reaction. Phase II reactions involve conjugation with endogenous substrates, such as acetate, glucuronic acid, glutathione, glycine, and sulfate. These reactions further increase the polarity of an intermediate metabolite, make the compound more water soluble and thereby enhance its renal excretion. Interindividual variability in drug biotransformation activity (for both phase I and phase II reactions) is a consequence of the complex interplay among genetic (genotype, sex, race or ethnic background) and environmental (diet, disease, concurrent medication, other xenobiotic exposure) factors. The pathway and rate of a given compound's biotransformation is a function of each individual's unique phenotype with respect to the forms and amounts of drug-metabolizing enzymes expressed.

The **CYP enzymes** are quantitatively the most important of the phase I enzymes. These heme-containing proteins catalyze the metabolism of many lipophilic endogenous substances (i.e., steroids, fatty acids, fat-soluble vitamins, prostaglandins, leukotrienes, and thromboxanes) as well as xenobiotic compounds, including a multitude of drugs and environment toxins. CYP nomenclature is based on evolutionary considerations and uses the root symbol CYP for cytochrome P450. CYP enzymes that share at least 40% homology are grouped into families denoted by an Arabic number after the CYP root. Subfamilies, designated by a letter, appear to represent clusters of highly related genes. Members of the human CYP2 family, for example, have >67% amino acid sequence homology. Individual P450s in a subfamily are numbered sequentially (e.g., CYP3A4, CYP3A5). CYP enzymes that have been identified as being important in human drug metabolism are predominantly found in the CYP1, CYP2, and CYP3 gene families. Importantly, enzyme activity may be induced or inhibited by various agents (see Table 59-2).

For most CYP enzymes, genotype–phenotype relationships are influenced by development in that fetal expression is limited (with the exception of CYP3A7) and functional activity is acquired postnatally in isoform-specific patterns.

**Phase II enzymes** include arylamine N-acetyltransferases (NAT1, NAT2), glucuronosyltransferases (UGTs), epoxide hydrolase, glutathione S-transferases, sulfotransferases, and methyltransferases (catechol O-methyltransferase, thiorurine S-methyltransferase, several N-methyltransferases). Like the CYPs, UGTs, sulfotransferases, and glutathione S-transferases are gene families with multiple individual isoforms, each having its own preferred substrates, mode of regulation, and tissue-specific pattern of expression.

Clearance of some compounds appears to be greater in children relative to adults and the correlation between genotype and phenotype in neonatal life through adolescence may be overridden by these developmental phenomena.

**CYP2D6**

The CYP2D6 gene locus is highly polymorphic, with more than 100 allelic variants identified to date (http://www.cypalleles.ki.se/cyp2d6.htm; see Table 59-2). Individual alleles are designated by the gene name (CYP2D6) followed by an asterisk, and an Arabic number. By convention, CYP2D6*1 designates the fully functional wild-type allele. Allelic variants are the consequence of point mutations, single base-pair deletions or additions, gene rearrangements, or deletion of the entire gene, resulting in a reduction or complete loss of activity. Inheritance of 2 recessive loss-of-function alleles results in the **poor-metabolizer phenotype**, which is found in approximately 5-10% of white subjects and approximately 1-2% of Asian subjects. In white subjects, the *3, *4, *5, and *6 alleles are the most common loss-of-function alleles and account for approximately 98% of poor-metabolizer phenotypes. In contrast, CYP2D6 activity on a population basis tends to be lower in Asian and African-American populations because of a lower frequency of nonfunctional alleles (*3, *4, *5, and *6) and a relatively high frequency of population-selective alleles that are associated with decreased activity relative to the wild-type CYP2D6*1 allele. The CYP2D6*10 allele occurs as a frequency of approximately 50% in Asians, whereas CYP2D6*17 and CYP2D6*29 occur at relatively high frequencies in subjects of black African origin.

CYP2D6 is involved in the biotransformation of more than 40 therapeutic entities, including several β-receptor antagonists, antiarrhythmics, antidepressants, antipsychotics, and morphine derivatives (for an updated list, see http://static.medicine.iupui.edu/divisions/clinpharm/content/p450_Table_Oct_11_2009.pdf; see Table 59-2). CYP2D6 substrates commonly encountered in pediatrics include selective serotonin inhibitors (SSRIs; fluoxetine, paroxetine, sertraline), risperidone, atomoxetine, promethazine, tramadol, and codeine. Furthermore, nonprescription cold remedies such as dextromethorphan, diphenhydramine, and chlorpheniramine are also CYP2D6 substrates. An analysis of CYP2D6 ontogeny in vitro that utilized a relatively large number of samples revealed that CYP2D6 protein and activity remain relatively constant after 1 wk of age up to 18 yr. Similarly, results from an in vivo longitudinal phenotyping study involving more than 100 infants over the 1st year of life demonstrated considerable interindividual variability in CYP2D6 activity, but no relationship between CYP2D6 activity and postnatal age between 2 wk and 12 mo of age. Furthermore, a cross-sectional study involving 586 children reported that the distribution of CYP2D6 phenotypes in children was comparable to that observed in adults by at least 10 yr of age. Thus, both available in vitro and in vivo data, albeit based on phenotype data rather than information on drug clearance from pharmacokinetic studies, imply that genetic variation is more important than developmental factors as a determinant of CYP2D6 variability in children.

One consequence of CYP2D6 developmental pharmacogenetics may be the syndrome of irritability, tachypnea, tremors, jitteriness, increased muscle tone, and temperature instability in neonates born to mothers receiving SSRIs during pregnancy. Controversy currently exists as to whether these symptoms reflect a neonatal withdrawal (hyposerotonergic) state or represent manifestations of serotonin toxicity analogous to the hyposerotonergic state associated with the SSRI-induced serotonin syndrome in adults (see Chapter 106.1). Delayed expression of CYP2D6 (and CYP3A4) in the 1st few wk of life is consistent with a hyposerotonergic state caused by delayed clearance of paroxetine and fluoxetine (CYP2D6) or sertraline (CYP3A4) in neonates exposed to these compounds during pregnancy. Furthermore, decreases in plasma SSRI concentrations and resolution of symptoms would be expected with increasing postnatal age and maturation of these pathways. Given that treatment of a “withdrawal” reaction may include administration of an SSRI, there is considerable potential for increased toxicity in affected neonates. Resolution of the question whether symptoms are caused by withdrawal vs a hyposerotonergic state is essential for appropriate management of SSRI-induced neonatal adaptation syndromes. Until further data are available, it is prudent to consider newborns and infants younger than 28 days of age as CYP2D6 genotypic poor metabolizers.

In older children, drug accumulation and resultant concentration-dependent toxicities in CYP2D6 genotypic poor metabolizers should be anticipated in the same way that they are in adults because of the risk of significant morbidity and mortality. Although a fluoxetine-related death has been reported in a 9 yr old child with a CYP2D6 poor metabolizer genotype, experience with paroxetine indicates that the risk of drug accumulation may also occur, under certain conditions, in individuals at the opposite end of the activity spectrum. The pharmacokinetics of paroxetine and nefazodone, both CYP2D6 substrates, correlate with the CYP2D6 phenotype in children and adolescents...
7-17 yr of age. However, chronic dosing of paroxetine may lead to greater-than-anticipated drug accumulation in children classified as CYP2D6 extensive metabolizers. In depressed children and adolescents, as well as in adults, there is a disproportionate increase in peak concentrations and area under the serum concentration–time curves at higher dose levels. However, nonlinearity is more prominent in patients who are CYP2D6 extensive metabolizers, especially those with gene duplications and 3 or more functional alleles. The largest decreases in paroxetine clearance observed with ascending doses are seen in patients who have the greatest clearance at the initial dose level (10 mg/day) and are predicted to have the greatest CYP2D6 activity based on CYP2D6 genotype. This seemingly paradoxical effect is best explained in the context of data from in vitro studies. One proposed mechanism involves oxidation of paroxetine within the CYP2D6 active site to form a reactive intermediate that is associated with irreversible modification of the CYP2D6 protein in or near the active site. In theory, the greater the initial CYP2D6 activity, the greater the burden of reactive metabolite burden that is formed and thereby an increased loss of CYP2D6 catalytic activity. As a consequence, as the paroxetine dose is increased in patients with higher initial drug clearance, the risk of excessive drug accumulation increases disproportionately.

Theoretically, younger children may experience decreased efficacy or therapeutic failure with drugs such as codeine and tramadol that are dependent on functional CYP2D6 activity for conversion to the pharmacologically active species. CYP2D6 catalyzes the O-demethylation of inactive codeine to active morphine. Infants and children appear capable of converting codeine to morphine and achieving morphine: codeine ratios comparable to those of adults. However, in one study, morphine and its metabolites were not detected in 36% of children receiving codeine, making the level of analgesia from codeine unreliable in the studied pediatric population. Interestingly, in this study levels of morphine and its metabolites were not related to CYP2D6 phenotypes. Finally, ultrarapid CYP2D6 metabolism of codeine may result in opiate intoxication, including maternal ultrarapid metabolism of codeine, which can result in high serum and breast milk concentrations of morphine and may have adverse effects in the breastfed neonate.

**CYP2C9**

Although several clinically useful compounds are substrates for CYP2C9 (http://static.medicine.iupui.edu/divisions/clinpharm/content/p450_Table_Oct_11_2009.pdf; see Table 59-2), the effects of allelic variation are most profound for drugs with a narrow therapeutic index, such as phenytoin, warfarin, and tolbutamide. In vitro studies show a progressive increase in CYP2C9 expression from 1-2% of mature levels in the 1st trimester to approximately 30% at term. Considerable variability (approximately 35-fold) in expression is apparent over the 1st 5 mo of life, with approximately one-half of the samples studied exhibiting values equivalent to those observed in adults. One interpretation of these data is that there is broad interindividual variability in the rate at which CYP2C9 expression is acquired after birth, and in general, the onsets of CYP2C9 activity in vivo, as inferred from pharmacokinetic studies of phenytoin in newborns, is consistent with the in vitro results. The apparent half-life of phenytoin is prolonged (approximately 75 hr) in preterm infants, but decreases to approximately 20 hr in term newborns. By 2 wk of age, the half-life has further declined to 8 hr. Concentration-dependent (saturable) metabolism of phenytoin, reflecting the functional acquisition of CYP2C9 activity, does not appear until approximately 10 days of age. The maximal velocity of phenytoin metabolism is reported to decrease from an average of 14 mg/kg/day in infants to 8 mg/kg/day in adolescents, which may reflect changes in the ratio of liver mass to total body mass observed over this period of development, as has been observed for warfarin.

At least 56 allelic variants of CYP2C9 have been reported, but not all have been evaluated for their functional consequences. The CYP2C9*2 allele is associated with approximately 5.5-fold decreased intrinsic clearance for S-warfarin relative to the wild-type enzyme. Allelic variations resulting in amino acid changes within the enzyme active site, such as the CYP2C9*3, CYP2C9*4, and CYP2C9*5 alleles, are associated with activities that are approximately 5% of the wild-type protein. Approximately one-third of the white population carries a variant CYP2C9 allele (*2 and *3 alleles, most commonly), whereas the *2 and *3 alleles are virtually nonexistent in African-American, Chinese, Japanese, and Korean populations. In contrast, the *5 allele has been detected in African-Americans, but not in white subjects. The risk of bleeding complications in patients treated with warfarin and with concentration-dependent toxicity in patients treated with phenytoin is most pronounced for individuals with a CYP2C9*5/*3 genotype.

Compared to adults, the pharmacogenetics of warfarin dosing has not been studied as extensively in children. In adults, genetic variation in CYP2C9 and the warfarin target, VKORC1, as well as patient age, sex and weight, can account for 50-60% of the variation in warfarin dose requirements. A large fraction of the source of variation is still unknown, but it may be at least partially attributed to interactions with other drugs and foods. Studies in children demonstrate that the contribution of VKORC1 and CYP2C9 genotypes to variability in warfarin dose to achieve a stable international normalized ratio is quite variable, ranging from <5% to approximately 30%, and in each study the contribution of age, or a developmental variable that correlates with age (e.g., height or weight) accounts for the largest amount of variability. The factors contributing to differences between children and adults, and especially among the published pediatric studies, are not clear at this time.

**CYP2C19**

In vitro, CYP2C19 protein and catalytic activity can be detected at levels representing 12-15% of mature values by 8 wk of gestation and remain essentially unchanged throughout gestation and at birth. Over the 1st 5 mo of postnatal age, CYP2C19 activity increases linearly. Adult levels are achieved by 10 yr of age, although variability in expression is estimated to be approximately 21-fold between 5 mo and 10 yr of age. The major source of this variability is likely pharmacogenetic in nature. The CYP2C19 poor-metabolizer phenotype (also known as mefenonyl hydroxylase deficiency) is present in 3-5% of the white population and 20-25% of Asians. Although 25 variant alleles have been reported to date, the 2 most common variant alleles, CYP2C19*2 and CYP2C19*3, result from single base substitutions that introduce premature stop codons and, consequently, truncated polypeptide chains that possess no functional activity. Despite consistent increases in CYP2C19 activity observed in vitro over the 1st 5 mo of life, the results of an in vivo phenotyping study with omeprazole in Mexican children revealed a broad range of activity and implied that 17% of infants younger than 4 mo of age could be classified as poor metabolizers (no poor metabolizers were detected beyond that point). In contrast, 20% of children 3-9 mo old were classified as ultrarapid metabolizers compared with 6% of infants 1-3 mo of age. Similarly, a series of studies investigating pantoprazole pharmacokinetics in newborns, children and adolescents has revealed that the apparent oral clearance of pantoprazole is independent of CYP2C19 genotype in the 1st 2-3 mo after birth, but poor metabolizers can be distinguished from extensive metabolizers after 4-6 mo of age. The pharmacokinetic parameters of omeprazole are comparable to those observed in adults are achieved by 2 yr of age.

CYP2C19 also plays an important role in the metabolism of lansoprazole. In Japanese adults treated with lansoprazole, amoxicillin, and clarithromycin for Helicobacter pylori infection, the eradication rate for CYP2C19 poor metabolizers (97.8%) and heterozygous extensive metabolizers (1 functional CYP2C19 allele; 92.1%) was significantly greater than that observed in homozygous extensive metabolizers (72.7%). Of the 35 patients in whom initial treatment did not eradicate H. pylori, 34 had at least 1 functional CYP2C19 allele and eradication could be achieved with higher lansoprazole doses in almost all cases. Given that the frequency of the functional CYP2C19*1 allele is considerably greater in white subjects (approximately 0.84 [84%]) compared with Japanese subjects (approximately 0.55 [55%]), eradication failure can be expected to occur more frequently in whites. Because
proton pump inhibitors are widely used in children, pharmacogenetic as well as developmental considerations should guide pediatric dosing strategies.

**CYP3A4, CYP3A5, and CYP3A7**

The CYP3A subfamily consists of 4 members in humans (CYPs 3A4, 3A5, 3A7, and 3A43) and is quantitatively the most important group of CYP enzymes in terms of human hepatic drug biotransformation. These isozymes catalyze the oxidation of many different therapeutic entities, several of which are of potential importance to pediatric practice (for an updated list, see http://static.medline.com/pdfs/chlpharm/content/p450_Table_Oct_11_2009.pdf; see Table 59-2). CYP3A7 is the predominant CYP isoform in fetal liver and can be detected in embryonic liver as early as 50-60 days' gestation. CYP3A4, the major CYP3A isoform in adults, is essentially absent in fetal liver, but increases gradually throughout childhood. Over the 1st 6 mo of life, CYP3A7 expression exceeds that of CYP3A4, although its catalytic activity toward most CYP3A substrates is rather limited compared with that of CYP3A4. CYP3A4 is also abundantly expressed in intestine, where it contributes significantly to the first-pass metabolism of orally administered drugs which are substrates (i.e., midazolam). CYP3A5 is polymorphically expressed and is present in approximately 25% of adult liver samples studied in vitro.

Several methods have been proposed to measure CYP3A activity. Using these various phenotyping probes, CYP3A4 activity has been reported to vary widely (up to 50-fold) among individuals, but the population distributions of activity are essentially unimodal and evidence for polymorphic activity has been elusive. Although 24 allelic variants have been identified to date (http://www.cypalleles.ki.se/cyp3a4.htm), most occur relatively infrequently and do not appear to be of clinical importance. Of interest to pediatrics is the CYP3A4*1B allele present in the CYP3A4 promoter region. The clinical significance of this allelic variant appears limited with respect to drug biotransformation activity, despite being associated with 2-fold increased activity over the wild-type CYP3A4*1 allele in in vitro assays. Although there does not appear to be an association between the CYP3A4*1B allele and age of menarche, a significant relationship does exist between the number of CYP3A4*1B alleles and the age at onset of puberty, as defined by Tanner breast score. In one study, 90% of 9 yr old girls with a CYP3A4*1B/*1B genotype had a Tanner breast score of ≥2 compared with 56% of CYP3A4*1A/*1B heterozygotes and 40% of girls homozygous for the CYP3A4*1A allele. Because CYP3A4 plays an important role in testosterone catabolism, the authors of the latter study proposed that the estradiol: testosterone ratio may be shifted toward higher values in the presence of the CYP3A4*1B allele and trigger the hormonal cascade that accompanies puberty. Intestinal CYP3A4 activity is inhibited by grapefruit juice and may result in higher levels of the many drugs metabolized by this enzyme; very large quantities of grapefruit juice may also inhibit the hepatic CYP3A4.

The CYP3A4*22 allele has received attention due to its association with reduced clearance of statins in adults as well as immunosuppressants, such as cyclosporine and tacrolimus, in children and adults. Improved response to inhaled fluticasone has also been reported in children and adults. N-acetyltransferase activity, such as N-acetylation of cyclosporine and tacrolimus, in children and adults. Improved response to inhaled fluticasone has also been reported in children and adults.

Polymorphic CYP3A5 expression is largely the result of a SNP in intron 3 that creates a cryptic splice site and gives rise to messenger RNA splice variants that retain part of intron 3 with a premature stop codon. The truncated messenger RNA transcripts associated with this allele, CYP3A5*3, cannot be translated into a functional protein. Individuals with at least 1 wild-type CYP3A5*1 allele express functional CYP3A5 protein, whereas those homozygous for CYP3A5*3 (CYP3A5*3/*3) do not express appreciable amounts of functional protein. Approximately 60% of African-Americans show functional hepatic CYP3A5 activity compared with only 33% of European Americans. Clinically important consequences of CYP3A5 allelic variation have been reported in children. In pediatric heart transplant patients with a CYP3A5*1/*3 genotype, tacrolimus concentrations were approximately 50% of those observed in patients with CYP3A5*3/*3 genotypes, when corrected for dose, 3 mo, 6 mo, and 12 mo after transplant. Thus, larger doses of tacrolimus are required in patients with functional CYP3A5 protein to achieve comparable blood levels and to minimize the risk of rejection.

**Glucuronosyltransferases**

The UGT gene superfamily catalyzes the conjugation (with glucuronic acid) of several drugs used clinically in pediatrics, including morphine, acetaminophen, nonsteroidal anti-inflammatory drugs, and benzodiazepines. The effect of development on glucuronidation capacity has been well described and is illustrated by hyperbilirubinemia, gray baby syndrome (the cardiovascular collapse associated with high doses of chloramphenicol in newborns), and the 3.5-fold increase in morphine clearance observed in premature neonates at 24-39 wk postconceptual age. As with the CYPs, there are multiple UGT isoforms, and the acquisition of functional UGT activity appears to be isoform- and substrate-specific.

UGT1A1 is the major UGT gene product responsible for bilirubin glucuronidation, and more than 100 genetic alterations have been reported (Table 59-3), most of which are rare and are more properly considered mutations rather than gene polymorphisms (see Chapters 102 and 357.1). Inheritance of 2 defective alleles is associated with reduced bilirubin-conjugating activity and gives rise to clinical conditions, such as Crigler-Najjar syndrome and Gilbert syndrome. More frequently occurring polymorphisms involve a dinucleotide (TA) repeat in the atypical TATA box of the UGT1A1 promoter. The wild-type UGT1A1*1 allele has 6 repeats (TA6), and the TA7 (UGT1A1*33), TA8 (UGT1A1*28), and TA9 (UGT1A1*34) variants are all associated with reduced activity. UGT1A1*28, the most frequent variant, is a contributory factor to prolonged neonatal jaundice. This variant is also associated with impaired glucuronidation and thus toxicity of the active metabolite, SN-38, of the chemotherapeutic agent irinotecan. Allelic variations in UGT1A7 and UGT1A9 are also associated with irinotecan toxicity in adults with colorectal cancer.

The consequences of allelic variation in the UGT2B family are less certain. The predominant routes of morphine elimination include biotransformation to the pharmacologically active 6-glucuronide and the inactive 3-glucuronide. 6-Glucuronide formation is almost exclusively catalyzed by UGT2B7, whereas several UGTs in the UGT1A subfamily and UGT2B7 both contribute to 3-glucuronide formation. Increased 6-glucuronide: morphine ratios have been reported in individuals homozygous for the SNPs constituting the UGT2B7*2 allele. Although individuals genotyped as UGT2B7*2/*2 may produce higher than anticipated concentrations of pharmacologically active morphine and its metabolites, prospective pharmacogenetic studies addressing phenotype-genotype correlations and the consequences of morphine analgesia have had conflicting results.

**Arylamine N-Acetyltransferases**

One of the earliest discovered and most widely recognized genetic polymorphisms is the NAT2 polymorphism. Approximately 50% of whites and African-Americans in North America are phenotypically slow metabolizers, placing a substantial number of individuals at increased risk for the development of adverse drug effects, such as sulfasalazine-induced hemolysis, hydrazine or arylamine-induced peripheral neuropathy, procainamide- or isoniazid-induced systemic lupus erythematosus, and Stevens-Johnson syndrome or toxic epidermal necrolysis associated with sulfonamide administration. NAT2 function is inherited in an autosomal dominant fashion, with the inheritance of 2 “slow” alleles required for expression of the slow metabolizer phenotype. The relative proportion of rapid and slow metabolizers varies considerably with ethnic or geographic origin. The percentage of slow acetylators among Canadian Eskimos is 5%, but it approaches 90% in some Mediterranean populations.

In vivo, with the use of caffeine as a phenotyping probe, all infants 0-55 days of age appear to be phenotypically slow acetylators, whereas 50% and 62% of infants 122-224 and 225-342 days of age, respectively, can be characterized as fast acetylators. Several independent studies indicate that maturation of the NAT2 phenotype occurs during the 1st yr of life. Phenotype-genotype discordance is likely to be most
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Table 59-3  Internet Resources for Pharmacogenetics and Pharmacogenomics

INTRODUCTION TO PHARMACOGENOMICS
http://learn.genetics.utah.edu/content/pharma/
http://pgrn.org/display/pgmwebsite/PGRN+Home
http://www.pharmgkb.org/

PHARMACOGENETICS: ALLELIC VARIANTS OF DRUG METABOLIZING ENZYMES
CYP2C9
http://www.cypalleles.ki.se/cyp2c9.htm
CYP2C19
http://www.cypalleles.ki.se/cyp2c19.htm
CYP2D6
http://www.cypalleles.ki.se/cyp2d6.htm
CYP3A4
http://www.cypalleles.ki.se/cyp3a4.htm
CYP3A5
http://www.cypalleles.ki.se/cyp3a5.htm
UGTs
http://www.pharmacogenomics.pha.ulaval.ca/cms/ugt_alleles/
NAT1 and NAT2
http://nat.mbg.duth.gr/

PHARMACOGENETICS: SUBSTRATES OF DRUG METABOLIZING ENZYMES
http://static.medicine.iupui.edu/divisions/clinpharm/content/p450_Table_Oct_11_2009.pdf

PHARMACOGENETICS-BASED DOSING GUIDELINES
Dosing guidelines incorporating pharmacogenetic data developed by the Clinical Pharmacogenetics Implementation Consortium are available on the National Guidelines Clearinghouse website a publicly accessible resource for evidence-based clinical guidelines sponsored by the Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health Services:
CYP2D6, CYP2C19, and tricyclic antidepressants
http://www.guideline.gov/content.aspx?id=43954
CYP2D6 and codeine
http://www.guideline.gov/content.aspx?id=39534
TPMT and thiopurines
http://www.guideline.gov/content.aspx?id=43955
HLA-B and allopurinol
http://www.guideline.gov/content.aspx?id=39536
HLA-B and abacavir
http://www.guideline.gov/content.aspx?id=39535
SLCO1B1 and simvastatin
http://www.guideline.gov/content.aspx?id=39537

*All sites were accessible on November 30, 2014.
HLA, human leukocyte antigen; TPMT, thiopurine methyltransferase.

Thiopurine S-Methyltransferase
Thiopurine S-methyltransferase (TPMT) is a cytosolic enzyme that catalyses the S-methylation of aromatic and heterocyclic sulfur-containing compounds, such as 6-mercaptopurine (6MP), azathioprine, and 6-thioguanine, used in the treatment of acute lymphoblastic leukemia (ALL), inflammatory bowel disease, juvenile arthritis, and for the prevention of renal allograft rejection. To exert its cytotoxic effects, 6MP requires metabolism to thioguanine nucleotides by a multistep process that is initiated by hypoxanthine guanine phosphoribosyl transferase. TPMT prevents thioguanine nucleotide production by methylating 6MP (Fig. 59-4A). TPMT activity is usually measured in erythrocytes, with activity in erythrocytes reflecting which is found in other tissues, including liver and leukemic blasts. Although approximately 89% of whites and African-Americans have high TPMT activity and 11% have intermediate activity, 1 in 300 individuals inherit TPMT deficiency as an autosomal recessive trait (Fig. 59-4B). In newborn infants, peripheral blood TPMT activity is reported to be 50% greater than in race-matched adults and shows a distribution of activity that is consistent with the polymorphism characterized in adults. There are no data currently to indicate how long this higher activity is maintained, although TPMT activities were comparable to previously reported adult values in a population of Korean schoolchildren age 7-9 yr. In patients with intermediate or low activity, more drug is shunted toward production of cytotoxic thioguanine nucleotides. TPMT can also methylate 6-thioinosine S’-monophosphate to generate a methylated metabolite that is capable of inhibiting de novo purine synthesis (Fig. 59-4C). Three mutations have been identified in the TPMT gene (*2, *3A, *3C), which account for 98% of white subjects with low activity. These mutations encode proteins that undergo rapid protelysis resulting in low enzyme activity.

TPMT*3A is the most common mutant allele and is characterized by 2 nucleotide transition mutations, G460A and A719G, that lead to 2 amino acid substitutions, Ala154Thr and Tyr240Cys (see Fig. 59-4D). Although the *3A allele only has a frequency of 0.03% in the general population, it represents 55% of all mutant alleles. Either mutation alone results in loss of functional activity through the production of unstable proteins that are subject to accelerated proteolytic degradation. Less-frequent allelic variants involve SNPs that produce amino acid substitutions in the coding region and defective intron–exon splicing. A polymorphic locus has been identified in the promoter region of the TPMT gene involving 4-8 repeats of a specific nucleotide sequence in tandem. Although these repeats appear to modulate TPMT activity when expressed in vitro, their role in regulating activity in vivo has not been clearly established.

The relatively few patients with low to absent TPMT activity (0.3%) are at increased risk for severe myelosuppression if treated with routine doses of thiopurines; thus, they require a 10–15-fold reduction in dose to minimize this risk. Furthermore, if not dosed properly, patients may be at increased risk for relapse as a result of inadequate or absent treatment with thiopurines. Given the expanding use of 6MP and azathioprine in pediatrics to treat inflammatory bowel disease and juvenile arthritis and to prevent renal allograft rejection, TPMT pharmacogenetics is not a trivial matter.

Introduction of the TPMT phenotype or genotype determination into pediatric practice will lead to safer, more efficacious treatment in pediatric patient groups. Although the majority of research has been conducted in patients with acute lymphoblastic leukemia, the observation that patients classified as having intermediate TPMT activity are more likely to be intolerant of 6MP or azathioprine and likely will require more frequent dosage reductions in response to drug-induced myelosuppression is equally applicable to other pediatric patient groups (i.e., patients with Crohn disease) treated with this family of drugs.

PHARMACOGENETICS OF DRUG TRANSPORTERS
There are several major types of membrane transporters, including organic anion transporter (OAT), organic anion transporting polypeptides (OATPs), organic cation transporting proteins (OCTs), and the adenosine triphosphate–binding cassette (ABC) transporters, such as P-glycoprotein and the multidrug-resistant proteins (MRPs).
Membrane transporters are heavily involved in drug disposition and actively transport substrate drugs between organs and tissues. Drug transporters are expressed at numerous epithelial barriers, such as intestinal epithelial cells, hepatocytes, renal tubular cells, and at the blood–brain barrier (Fig. 59-5). Transporters often are also determinants of drug resistance, and many drugs work by affecting the function of transporters. As such, polymorphisms in the genes encoding these proteins may have a significant effect on the absorption, distribution, metabolism, and excretion as well as the pharmacodynamic effect of a wide variety of compounds.

The Adenosine Triphosphate–Binding Cassette Superfamily

The ABC transporters belong to the largest known transporter gene family and translocate a variety of substrates, including chemotherapy agents. ABC multidrug transporter expression is implicated in tumor cell resistance to anticancer therapy, altered disposition of chemotherapy drugs, and toxic side effects associated with chemotherapy. More recently, the genetic heterogeneity of a number of the ABC transporter genes has been described. Apart from having at least 1 adenosine triphosphate (ATP)-binding domain, these transporters are...
**DURING GROWTH AND DEVELOPMENT**

**CHANNELS, AND OTHER DRUG TARGETS**

**POLYMORPHISMS IN DRUG RECEPTORS, ION CHANNELS, AND OTHER DRUG TARGETS DURING GROWTH AND DEVELOPMENT**

**PHARMACOGENETICS OF DRUG RESPONSE: POLYMORPHISMS IN DRUG RECEPTORS, ION CHANNELS, AND OTHER DRUG TARGETS DURING GROWTH AND DEVELOPMENT**

Receptors are the targets for drugs and endogenous transmitters because of their inherent molecular recognition sites. Drugs and transmitters bind to the receptor to produce a pharmacologic effect. Variability in the receptor protein or the ion channel may determine the magnitude of the pharmacologic response. For example, polymorphisms of the β₂-adrenergic receptor gene (*ADRB2*) are associated with variable responses to bronchodilator drugs.

Drug responses are seldom monogenic events because multiple genes are involved in both drug binding to the pharmacologic target and the subsequent downstream signal transduction events that ultimately collectively manifest as a therapeutic effect. Although genotypes at a particular locus may show a statistically significant effect on the outcome of interest, they may account for only a relatively small amount of the overall population variability for that outcome. For example, a particular group of SNPs in the corticotropin-releasing hormone receptor 1 (*CRHR1*) gene is associated with a statistically...
Figure 59-6 Polygenic determinants of drug response. The potential effects of 2 genetic polymorphisms are illustrated. In each panel, there is a profile for subjects who have 2 wild-type alleles (WT/WT), those who are heterozygous for 1 wild-type and 1 variant (V) allele (WT/V), and those who have 2 variant alleles (V/V) for the depicted gene. The top panel illustrates a potential polymorphism involving a drug-metabolizing enzyme where variant alleles result in decreased drug metabolism and greater exposure (as shown by the increasing area under the concentration-time curve [AUC]). The second panel illustrates a potential polymorphism involving a drug receptor and depicts variant alleles which result in decreased receptor sensitivity. Note that for each receptor type, there are 3 possibilities for drug exposure. At the bottom is a table that shows the 9 resulting combinations of drug-metabolism and drug-receptor genotypes and the corresponding drug-response phenotypes calculated from data shown in the second panel. These phenotypes allow for calculation of a therapeutic index (i.e., efficacy:toxicity, in this example these range from 13 [65%:5%] to 0.1 [10%:80%]), which results in the ability to perform an individualized risk:benefit assessment. (Adapted from Evans WE, McLeod HL: Pharmacogenomics—drug disposition, drug targets, and side effects. N Engl J Med 348:538–549, 2003.)
significant improvement in forced expiratory volume in 1 sec, but accounts for only 6% of the overall variability in response to inhaled corticosteroids (see Chapter 144). A series of subsequent studies has determined that allelic variation in several genes in the steroid pathway contributes to overall response to this form of therapy.

The listing and classification of receptors is a major initiative of the International Union of Pharmacology. The list of receptors and voltage-gated ion channels is available on the International Union of Pharmacology website (http://www.guidetopharmacology.org/).

CURRENT AND FUTURE APPLICATIONS FOR PHARMACOGENETICS AND PHARMACOGENOMICS IN PEDIATRICS

Progress being made in the treatment of ALL provides an outstanding example of how the application of pharmacogenomic principles can improve pediatric drug therapy (see Chapter 495). Despite improved understanding of the genetic determinants of drug response, however, many complexities remain to be resolved. Patients with ALL who have 1 wild-type allele and intermediate TPMT activity tend to have a better response to 6MP therapy than patients with 2 wild-type alleles and full activity. Reduced TPMT activity also places patients at risk for irradiation-induced secondary brain tumors and etoposide-induced acute myeloid leukemias. Pharmacogenetic polymorphisms of several additional genes also have the potential to influence successful treatment of ALL. Multiple genetic and treatment-related factors interact to create patient subgroups with varying degrees of risk, and these represent an opportunity for pharmacogenomic approaches to identify subgroups of patients who will benefit from specific treatment regimens and those who will be at risk for short- and long-term toxicities (Fig. 59-6).

The 20% of patients with ALL who do not respond to chemotherapy represent an additional challenge for pharmacogenomic research. Gene expression (microarray) studies in ALL blasts are able to discriminate among phenotypic subtypes and identify some individuals who are at risk for treatment failure. An analysis of acute treatment-induced changes in the gene response of ALL blasts obtained 1 day after the initiation of 6MP and methotrexate as single agents or in combinations of high-dose or low-dose methotrexate and 6MP showed several important insights into the cellular response to these treatments. Changes in gene expression were treatment-specific and could accurately discriminate among the 4 treatments. ALL cells of different molecular subtypes shared common cellular responses to treatment, suggesting that it may be possible to personalize treatment strategies in ALL.

Bibliography is available at Expert Consult.
Chapter 59: Pediatric Pharmacogenetics, Pharmacogenomics, and Pharmacoproteomics

Bibliography


The clinical pharmacology of a given drug reflects a multifaceted set of properties that pertain to its disposition and action, and the response (e.g., adverse effects, therapeutic effects, and therapeutic outcome) to their administration/use. The 3 most important facets of the clinical pharmacology of a drug are its pharmacokinetics, pharmacodynamics, and the role of genetic variability as it may impact drug disposition or action (i.e., pharmacogenomics) (see Chapter 59).

Pharmacokinetics describes the movement of a drug throughout the body and the concentrations (or amounts) of a drug that reach a given body space and/or tissue and its residence time therein. Pharmacokinetics of a drug are conceptualized by considering those characteristics which collectively, are the determinants of the dose–concentration–effect relationship; namely, absorption, distribution, metabolism and excretion. Pharmacodynamics describes the relationship between drug dose or drug concentration and response. The response may be desirable (effectiveness) or untoward (toxicity). Although in clinical practice the response to drugs in different patient populations is often described by a standard dosing or concentration range, response is best conceptualized along a continuum where the relationship between dose and response(s) are not linear. Pharmacogenetics is the study of how variant forms of human genes contribute to interindividual variability in either drug disposition (e.g., variant alleles of gene controlling the expression of a drug transporter) and/or response (e.g., variant alleles altering the drug–receptor interaction). The finding that drug responses can be influenced by the patient’s genetic profile has offered great hope for realizing individualized pharmacotherapy when the relationship between genotype and phenotype (either disease and/or drug response) is predictive of drug response (see Chapter 59). In the developing child, it is apparent ontogeny that has the potential of modulating drug response through altering both pharmacokinetics and pharmacodynamics.

**GENERAL PHARMACOKINETIC AND PHARMACODYNAMIC PRINCIPLES**

Drug effect is produced only when an exposure (both amount and duration) occurs that is sufficient to produce a drug–receptor interaction capable of modulating the cellular milieu and inducing a biologic response. Thus, exposure–response relationships for a given drug represent an interface between pharmacokinetics and pharmacodynamics that can be simply conceptualized by consideration of 2 profiles: (1) plasma concentration vs effect (Fig. 60-1) and (2) plasma concentration vs time (Fig. 60-2).

The relationship between drug concentration and effect for most drugs is not linear (see Fig. 60-1). At a drug concentration of zero, the effect from the drug is generally zero or not perceptible (E0). Following drug administration and/or with dose escalation, the concentration increases as does the effect; first in an apparent linear fashion (at low drug concentrations) followed by a nonlinear increase in effect to an asymptotic point in the relationship where a maximal effect (Emax) is attained that does not perceptibly change with further increases in

*Figure 60-1 Plasma concentration vs effect curve. The percent effect is measured as a function of increasing drug concentration in the plasma. The dose at which no effect is seen in the population is E0. The dose of a drug required to produce a specified effect in 50% of the population is abbreviated as EC50. The concentration associated with the maximal effect that can be produced by a drug is abbreviated as Emax. (From Abdel-Rahman SM, Kearns GL. The pharmacokinetic-pharmacodynamic interface: determinants of anti-infective drug action and efficacy in pediatrics. In Feigin RD, Cherry JD, Demmler-Harrison GJ, Kaplan SL, editors, Textbook of pediatric infectious disease, ed 6, Philadelphia, 2009, WB Saunders, pp. 3156–3178, reproduced with permission.)*
Figure 60-2 Semilogarithmic plot of the plasma concentration vs time curve for a hypothetical drug following extravascular administration. The area under the plasma level-time curve (AUC) is a concentration and time-dependent measure of systemic drug exposure. After administration, the drug is absorbed and reaches the maximal concentration (C_{max}) at its peak time (T_{max}). Following completion of drug absorption and distribution, plasma drug concentrations decline in an apparent monoexponential fashion whereby the slope of the apparent elimination phase represents the apparent elimination rate constant (ke). (From Abdel-Rahman SM, Kearns GL. The pharmacokinetic-pharmacodynamic interface: determinants of anti-infective drug action and efficacy in pediatrics. In Feigin RD, Cherry JD, Demmler-Harrison GJ, Kaplan SL, editors. Textbook of pediatric infectious disease, ed 6, Philadelphia, 2009, WB Saunders, pp. 3156–3178, reproduced with permission.)

Drugs that may be in a given drug class. In practice, Emax can be derived from visual interpolation of the concentration–effect profile or either from mathematical curve fitting of the relationship.

Because it is rarely possible to measure drug concentrations at or near the receptor, it is necessary to utilize a surrogate measurement to assess exposure–response relationships. In most instances, this surrogate is represented by the plasma drug concentration vs time curve. For drugs whose pharmacokinetic properties are best described by 1st-order (as opposed to zero-order or mixed-order) processes, a semilogarithmic plot of plasma drug concentration vs time data for an agent given by an extravascular route of administration (e.g., intramuscular, subcutaneous, intracisternal, peroral, transmucosal, transdermal, rectal) produces a pattern similar to that illustrated by Figure 60-2. The ascending portion of this curve represents a time during which the liberation of a drug from its formulation, dissolution of the drug in a biologic fluid (e.g., gastric or intestinal fluid, interstitial fluid; a prerequisite for absorption) and absorption of a drug are rate-limiting relative to its elimination. After the time (T_{max}) where maximal plasma concentrations (C_{max}) are observed, the plasma concentration decreases as metabolism and elimination become rate limiting; the terminal portion of this segment of the plasma concentration vs time curve being representative of drug elimination from the body. Finally, the area under the plasma concentration vs time curve (AUC), a concentration- and time-dependent parameter reflective of the degree of systemic exposure from a given drug dose, can be determined by integrating the plasma concentration data over time. By being able to characterize the pharmacokinetics of a specific drug, the clinician can use the data to individualize dosing regimens for patients who by virtue of development and/or disease, must have adjustments to either the dose and/or dosing interval so as to enable the production of the degree of systemic exposure associated with desired pharmacologic effects. For drugs where a therapeutic plasma concentration range and/or “target” systemic exposure (i.e., AUC) is known, a priori knowledge of pharmacokinetic parameters for a given population or patient within a population can facilitate the selection of a drug dosing regimen. When linked with information regarding the pharmacodynamic behavior of a drug and the status of the patient (e.g., age, organ function, disease state, concomitant medications), the application of pharmacokinetics affords the practitioner the ability to exercise some real degree of adaptive control over therapeutic decision making by enabling the selection of a drug and dosing regimen that has the greatest likelihood of producing both efficacy and safety.

THE IMPACT OF ONTOGENY ON DRUG DISPOSITION

Development represents a continuum of biologic events that enable adaptation, somatic growth, neurobehavioral maturation and eventually reproduction. The impact of development on the pharmacokinetics of a given drug is determined, to a great degree, by age-related changes in body composition and the acquisition of function in organs and organ systems, which are important in determining drug metabolism and excretion. Even though it is often convenient to classify pediatric patients on the basis of postnatal age for the provision of drug therapy (e.g., neonate 0–1 mo of age; infant 1–24 mo of age; children 2–12 yr of age; and adolescents 12–18 yr of age), it is important to recognize that the changes in physiology are not linearly related to age and may not correspond to these age-defined breakpoints. In fact, the most dramatic changes in drug disposition occur during the 1st 18 mo of life where the acquisition of organ function is most dynamic. Additionally, it is important to note that the pharmacokinetics of a given drug may be altered in pediatric patients consequent to intrinsic (e.g., gender, genotype, ethnicity, inherited diseases) or extrinsic (e.g., acquired disease states, xenobiotic exposure, diet, variability in therapeutic adherence) factors that may occur during the 1st 2 decades of life.

During development, certain stages of life profoundly influence drug response and disposition. Dramatic pharmacokinetic, pharmacodynamic, and psychosocial changes occur as preterm infants mature toward term, as infants mature through the 1st 5 years of life, and as children reach puberty and adolescence (Fig. 60-3). It is most useful to conceptualize the impact of ontogeny on drug disposition by considering its specific facets, namely, drug absorption, distribution, metabolism, and excretion, as well as ontogeny’s impact on drug action (pharmacodynamics).

Drug Absorption

Absorption usually occurs via passive diffusion, but active transport or facilitated diffusion also may be necessary for drug entry into cells. Several physiologic factors affect this process, 1 or more of which may be altered in the face of certain disease states (e.g., inflammatory bowel disease, diarrhea) and, consequently, produce changes in drug bioavailability. The rate and extent of absorption can be significantly affected as a consequence of a child’s normal growth and development.

Peroral Absorption

The most important factors that influence drug absorption from the gastrointestinal tract are related to the physiology of the stomach, intestine, and biliary tract (see Fig. 60-3C and Table 60-1). The rate and extent of peroral absorption of drugs depends primarily on the pH-dependent passive diffusion and motility of the stomach and intestinal tract as both of these factors will influence transit time of the drug. Gastric pH changes significantly throughout development with the highest (alkaline) values occurring during the neonatal period. In the fully mature neonate, the gastric pH ranges from 6–8 at birth and drops to 2–3 within a few hours of birth. However, after the 1st 24 hr of life, the gastric pH drifts upward because of the immaturity of the parietal cells. As the parietal cells mature, the gastric acid secretory capacity increases (pH decreases) over the 1st few months of life to reach consistent adult levels by 3–7 yr of age. As a result, the peroral bioavailability of acid-labile drugs, such as penicillin or ampicillin, is increased. In contrast, the absorption of weak organic acids (e.g., phenobarbital and phenytoin) is relatively decreased, a condition which may necessitate the administration of larger doses in the very young to achieve therapeutic plasma levels.
changes in gastrointestinal motility. In older infants and young children, more rapid rates of intestinal drug transit can reduce the bioavailability for some drugs (e.g., phenytoin) and/or drug formulations (e.g., sustained-release) by reducing their residency time at the absorption surfaces in the small intestine.

Lastly, neonates, particularly premature neonates, have a reduced bile acid pool and biliary function resulting in a decreased ability to solubilize and absorb lipophilic drugs. Even though biliary function

Gastric emptying time is prolonged throughout infancy and childhood consequent to reduced motility which may retard drug passage into the intestine where the majority of absorption takes place. Gastric emptying rates reach or exceed adult values by 6-8 mo of life. As such, intestinal motility is important for the rate of drug absorption and, like other factors, is dependent on the age of the child. Consequently, the rate of absorption of drugs with limited water solubility (e.g., phenytoin, carbamazepine) can be dramatically altered consequent to

Figure 60-3 Developmental changes in physiologic factors that influence drug disposition in infants, children, and adolescents. Physiologic changes in multiple organ systems during development are responsible for age-related differences in drug disposition. A, As this graph shows, the activity of many cytochrome P450 (CYP) isoforms and a single glucuronosyltransferase (UGT) isoform is markedly diminished during the 1st 2 mo of life. In addition, the acquisition of adult activity over time is enzyme- and isoform-specific. B, This chart shows age-dependent changes in body composition that influence the apparent volume of distribution of drugs. Infants in the 1st 6 mo of life have markedly expanded total-body water and extracellular water, expressed as a percentage of total-body weight, as compared with older infants and adults. C, This graph summarizes the age-dependent changes in both the structure and function of the gastrointestinal tract. As with hepatic drug-metabolizing enzymes (A), the activity of CYP1A1 in the intestine is low during early life. D, This chart shows the effect of postnatal development on the processes of active tubular secretion—represented by the clearance of paraaminohippuric acid and the glomerular filtration rate, both of which approximate adult activity by 6-12 mo of age. E, This graph shows age dependence in the thickness, extent of perfusion, and extent of hydration of the skin and the relative size of the skin-surface area (reflected by the ratio of body surface area to body weight). Although skin thickness is similar in infants and adults, the extent of perfusion and hydration diminishes from infancy to adulthood. (From Kearns GL, Abdel-Rahman SM, Alander SW, et al, Developmental pharmacology—drug disposition, action, therapy in infants and children. N Engl J Med 349:1157–1167, 2003. Reproduced with permission.)
Principles
Developmental Alteration in Intestinal Drug Absorption

<table>
<thead>
<tr>
<th>PHYSIOLOGIC ALTERATION</th>
<th>NEONATE</th>
<th>INFANTS</th>
<th>CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric pH</td>
<td>&gt;5</td>
<td>4-2</td>
<td>Normal (2-3)</td>
</tr>
<tr>
<td>Gastric emptying time</td>
<td>Irregular</td>
<td>Increased</td>
<td>Slightly increased</td>
</tr>
<tr>
<td>Intestinal motility</td>
<td>Reduced</td>
<td>Increased</td>
<td>Slightly increased</td>
</tr>
<tr>
<td>Intestinal surface area</td>
<td>Reduced</td>
<td>Near adult</td>
<td>Adult pattern</td>
</tr>
<tr>
<td>Microbial colonization</td>
<td>Reduced</td>
<td>Near adult</td>
<td>Adult pattern</td>
</tr>
<tr>
<td>Biliary function</td>
<td>Immature</td>
<td>Near adult</td>
<td>Adult pattern</td>
</tr>
</tbody>
</table>

Direction of alteration given relative to expected normal adult pattern.


Develops in the 1st few months of life, it may be difficult for the neonate and young infant to absorb fat-soluble vitamins as low concentrations of bile acids are necessary for their absorption.

Extravascular Drug Absorption

With a bioavailability of 100%, intravenous drug administration is assumed to be the most dependable and accurate route for drug delivery. Absorption of drugs from tissues and organs (e.g., intramuscular, transdermal, and rectal) can also be affected by development (Table 60-2). Intramuscular blood flow changes with age, which can result in variable and unpredictable absorption. Reduced muscular blood flow in the 1st few days of life, the relative inefficiency of muscular contractions (useful in dispersing an IM drug dose), and an increased percentage of water per unit of muscle mass may delay the rate and/or extent of drugs given intramuscularly to the neonate. Muscular blood flow increases into infancy and, consequently, the bioavailability of drugs given by the IM route is comparable to that seen in children and adolescents.

In contrast, mucosal permeability (rectal and buccal) in the neonate is increased and thus, may result in enhanced absorption by this route. Transdermal drug absorption in the neonate and very young infant is increased as the result of a more hydrated stratum corneum (see Fig. 60-3C). In addition, the ratio of body surface area to body weight is greater in infants and children compared to adults. Collectively, these developmental differences may predispose the child to increased exposure and risk for toxicity for drugs/chemicals placed on the skin (e.g., silver sulfadiazine, topical corticosteroids, benzocaine, diphenhydramine) with higher likelihood of occurrence during the 1st 12 mo of life.

Normal developmental differences in drug absorption from most all extravascular routes of administration can influence the dose-plasma concentration relationship in a manner sufficient to alter pharmacodynamics. It should be recognized that the presence of disease states which influence a physiologic barrier for drug absorption and/or the time that a drug spends at a given site of absorption can further influence drug bioavailability and effect.

Drug Distribution

Drug distribution is influenced by a variety of drug-specific physiochemical factors (e.g., molecular size and weight, apparent partition coefficient, pKa), the presence of drug transporters, blood/tissue protein binding, blood and tissue pH1 and perfusion. However, age-related changes to drug distribution are primarily related to developmental changes in body composition and the quantity of plasma proteins capable of drug binding. Age-dependent changes in the relative sizes of body water (total body water [TBW], extracellular water) and fat compartments may alter the apparent volume of distribution (VD) for a given drug. The absolute amounts and distribution of body water and fat depend on a child's age and nutritional status. As well, certain disease states (e.g., ascites, dehydration, burn injuries, disruption of the integument involving large surface area) can influence body water compartment sizes and thereby, further impact the VD for certain drugs.

Newborns have a much higher proportion of body mass in the form of water (~75% TBW) than older infants and children (see Fig. 60-3B). As well, the percent of extracellular water changes (decreases) from the newborn stage (approximately 45%) into adulthood (approximately 20–30%). In fact, the increase of TBW in the neonate is attributable to extracellular water. The reduction in TBW is rapid in the 1st year of life with adult values (approximately 55%) achieved by approximately 12 yr of age. In contrast, the percentage of intracellular water as a function of body mass remains stable from the 1st months of life through adulthood. The impact of developmental changes in body water spaces are exemplified by drugs such as the aminoglycoside antibiotics; compounds that distribute predominantly throughout the extracellular fluid space and have a higher VD (0.4-0.7 L/kg) in neonates and infants as compared to adults (0.2-0.3 L/kg).

Body fat percentage and composition increase during normal development. The body fat percentage in a neonate is approximately 16% (57% water and 35% lipid). Despite the relatively low body fat content in the neonate, it is important to note that the lipid content in the developing central nervous system (CNS) is high, which has implications for the distribution of lipophilic drugs and their CNS effects (e.g., propranolol) during this time period. The body fat percentage tends to increase up to approximately 10 yr of age and then changes composition with respect to puberty and sex to approach adult body fat composition (26% water and 71% lipid). In addition, a sex difference exists as the child ages into adolescence. The total body fat in males is reduced by 50% between 10 and 20 yr of life as compared to females in whom the reduction is approximately 25%.

Albumin, total proteins, and total globulins (e.g., α1-acid glycoprotein) are the most important circulating proteins responsible for drug binding in plasma. The absolute concentration of these proteins is influenced by age, nutrition, and disease (Table 60-3). The concentrations of most all circulating plasma proteins are reduced in the neonate and young infant (approximately 80% of adult) and reach adult values by 1 year of age. A similar pattern of maturation is observed with α1-acid glycoprotein (an acute-phase reactant capable of binding basic drugs) where neonatal plasma concentrations are approximately 3 times lower than in maternal plasma and attain adult values by approximately 1 year of age.

The extent of drug binding to proteins in the plasma may influence distribution characteristics. Only free, unbound drug can be distributed from the vascular space into other body fluids and, ultimately, to tissues where drug–receptor interaction occurs. Drug protein binding depends on a number of age-related variables, which can include the absolute amount of proteins and their available binding sites; the conformational structure of the binding protein (e.g., reduced binding of

<table>
<thead>
<tr>
<th>PHYSIOLOGIC ALTERATION</th>
<th>NEONATE</th>
<th>INFANTS</th>
<th>CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral absorption</td>
<td>Erratic</td>
<td>Increased</td>
<td>Near adult</td>
</tr>
<tr>
<td>Intramuscular absorption</td>
<td>Variable</td>
<td>Increased</td>
<td>Near adult</td>
</tr>
<tr>
<td>Percutaneous absorption</td>
<td>Increased</td>
<td>Increased</td>
<td>Near adult</td>
</tr>
<tr>
<td>Rectal absorption</td>
<td>Very efficient</td>
<td>Efficient</td>
<td>Near adult</td>
</tr>
</tbody>
</table>

Direction of alteration given relative to expected normal adult pattern.


Table 60-1

Table 60-2

Table 60-1: Developmental Alteration in Intestinal Drug Absorption

Table 60-2: Influence of Ontogeny on Drug Absorption
Factors Influencing Drug Binding in Pediatrics

<table>
<thead>
<tr>
<th>PHYSIOLOGIC ALTERATION</th>
<th>NEONATE</th>
<th>INFANTS</th>
<th>CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma albumin</td>
<td>Reduced</td>
<td>Near adult</td>
<td>Near adult</td>
</tr>
<tr>
<td>Fetal albumin</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Total proteins</td>
<td>Reduced</td>
<td>Decreased</td>
<td>Near adult</td>
</tr>
<tr>
<td>Total globulins</td>
<td>Reduced</td>
<td>Decreased</td>
<td>Near adult</td>
</tr>
<tr>
<td>Serum bilirubin</td>
<td>Reduced</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Serum free fatty acids</td>
<td>Reduced</td>
<td>Increased</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Direction of alteration given relative to expected normal adult pattern.


Impact of Development on Drug Metabolism

<table>
<thead>
<tr>
<th>PHYSIOLOGIC ALTERATION</th>
<th>NEONATE</th>
<th>INFANTS</th>
<th>CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytochrome P450 activity</td>
<td>Reduced</td>
<td>Increased</td>
<td>Slightly increased</td>
</tr>
<tr>
<td>Phase II enzyme activity</td>
<td>Reduced</td>
<td>Increased</td>
<td>Near adult</td>
</tr>
<tr>
<td>Blood esterase activity</td>
<td>Reduced</td>
<td>Normal (by 1 yr)</td>
<td>Adult pattern</td>
</tr>
<tr>
<td>Presystemic enzyme activity</td>
<td>Reduced</td>
<td>Increased</td>
<td>Near adult</td>
</tr>
</tbody>
</table>

Direction of alteration given relative to expected normal adult pattern.


Acidic drugs to glycated albumin in patients with poorly controlled diabetes mellitus; the affinity constant of the drug for the protein; the influence of pathophysiologic conditions that either reduce circulating protein concentrations (e.g., ascites, major burn injury, chronic malnutrition, hepatic failure) or alter their structure (e.g., diabetes, uremia); and the presence of either endogenous or exogenous substances, which may compete for protein binding.

Developments associated with changes in drug binding can occur as a consequence of altered protein concentrations and/or binding affinity. For example, circulating fetal albumin in the neonate has significantly reduced binding affinity for acid drugs such as phenytoin, which is extensively (94-98%) bound to albumin in adults as compared to 80–85% in the neonate. The resultant 6-8-fold difference in the free fraction can result in CNS adverse effects in the neonate when total plasma phenytoin concentrations are within the generally accepted “therapeutic range” (10-20 mg/L). The importance of reduced drug-binding capacity of albumin in the neonate is exemplified by interactions between endogenous ligands (e.g., bilirubin, free fatty acids) and drugs with greater binding affinity (e.g., the ability of sulfonamides to produce kernicterus).

Drug transporters, such as P-glycoprotein, MDR1, and MDR2 (multidrug resistance 1 or 2), can influence drug distribution. These drug transporters can markedly influence the extent to which drugs cross membranes in the body and whether drugs can penetrate or are secreted from the target sites (inside cancer cells or microorganisms, or crossing the blood–brain barrier). Thus, drug resistance to cancer chemotherapy, antibiotics, or epilepsy may be conferred by these drug transport proteins and their effect on drug distribution. While there are limited data on the ontogeny of drug transport proteins, available information demonstrates their presence as early as 22 wk gestation and low levels in the neonatal period which appear to rapidly increase to adult values by 1-2 yr of age.

Drug Metabolism

Metabolism reflects the biotransformation of an endogenous or exogenous molecule by 1 or more enzymes to moieties that are more hydrophilic and thus, can be more easily eliminated by excretion, secretion, or exhalation. Although metabolism of a drug generally reduces its ability to produce a pharmacologic action, it can result in metabolites that have significant potency, thereby contributing to the overall pharmacodynamic profile of a drug (e.g., biotransformation of the tricyclic antidepressant amitriptyline to nortriptiline; cefotaxime to desacetylcefotaxime; theophylline to caffeine) or in some instances, can produce significant toxicity (e.g., biotransformation of codeine to morphine). In the case of prodrugs (e.g., zidovudine, enalapril, fosphenytoin) or some drug salts/esters (e.g., cefuroxime axetil, clindamycin phosphate), biotransformation is required to produce a pharmacologically active moiety. Finally, for some drugs, cellular injury and associated adverse reactions are the result of drug metabolism (e.g., acetaminophen hepatotoxicity, Stevens-Johnson syndrome associated with sulfamethoxazole).

The primary organ responsible for drug metabolism is the liver, although the kidney, small intestine, lung, adrenals, blood (phosphatases, esterases) and skin can also biotransform certain compounds. Drug metabolism occurs primarily in the endoplasmic reticula of cells via 2 general classes of enzymatic processes: phase I, or nonsynthetic, and phase II, or synthetic, reactions. Phase I reactions include oxidation, reduction, hydrolysis, and hydroxylation reactions, whereas phase II reactions primarily involve conjugation with an endogenous ligand (e.g., glycine, glucuronide, glutathione or sulfate). As illustrated by Figure 60-3A, many drug metabolizing enzymes demonstrate an ontogenetic profile with generally low activity present at birth and maturation over a period of months to years (Table 60-4).

Even though there are many enzymes that are capable of catalyzing the biotransformation of drugs and xenobiotics, the quantitatively most important are represented by the cytochromes P450 (CYPs), a supergene family with at least 16 primary enzymes. The specific CYP isoforms responsible for the majority of human drug metabolism are represented by CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. These enzymes represent the products of genes that in some instances, are polymorphically expressed with allelic variants producing enzymes generally resulting in either no or reduced catalytic activity (a notable exception being the *17 allele of CYP2C19 which conveys increased activity) (see Chapter 59). At birth, the concentration of drug-oxidizing enzymes in fetal liver (corrected for liver weight) appears similar to that in adult liver. However, the activity of these oxidizing enzymes is reduced, which results in slow clearance (and prolonged elimination) of many drugs that are substrates for them (e.g., phenytoin, caffeine, diazepam, and many others). Postnatally, the hepatic CYPs appear to mature at different rates. Within hours after birth, CYP2E1 activity increases rapidly with CYP2D6 being detectable soon thereafter. CYP2C (CYP2C9 and CYP2C19) and CYP3A4 are present within the 1st mo of life, and a few months later, CYP1A2. CYP3A4 activity in young infants may exceed that observed in adults as reflected by the clearance of drugs that are substrates for this enzyme (e.g., cyclosporine, tacrolimus).

Compared to phase I drug-metabolizing enzymes, the impact of development on the activity of phase II enzymes (acetylation, glucuronidation, sulfation) is not characterized as well. Generally speaking, phase II enzyme activity is decreased in the newborn and increases into childhood. For example, conjugation of compounds metabolized by isozymes of glucuronosyltransferase (UGT; e.g., morphine, bilirubin, and chloramphenicol) is reduced at birth but can exceed adult values by 3-4 yr of age. Also, the ontogeny of UGT expression is isozyme specific. Newborns and infants primarily metabolize the commonly used analgesic acetaminophen by sulfate conjugation whereas the UGT isozymes responsible for its glucuronidation (UGT1A1 and UGT1A9) have markedly reduced activity. As children age, the
Renal Drug Elimination

The kidney is the primary organ responsible for the excretion of drugs and their metabolites. The development of renal function begins during early fetal development and is complete by early childhood (see Fig. 60-3D, Table 60-5). Total renal drug clearance (CLrenal) can be conceptualized by considering the following equation:

\[
CL_{\text{renal}} = (\text{GFR} + \text{ATS}) - \text{ATR}
\]

where glomerular filtration rate (GFR), active tubular secretion (ATS), and active tubular reabsorption (ATR) of drugs can contribute to overall clearance. As is true for hepatic drug metabolism, only free (unbound) drug and/or metabolite can be filtered by a normal glomerulus and/or either secreted or reabsorbed via a renal tubular transport proteins.

Renal clearance is limited in the newborn by both anatomical and functional immaturity of the nephron unit. In both the term and preterm neonate, GFR averages 2-4 mL/min/1.73 m² at birth. During the 1st few days of life, a drop in renal vascular resistance occurs which results in a net increase in renal blood flow and a re-distribution of intrarenal blood flow from a predominantly medullary to a cortical distribution. All of these changes are associated with a commensurate increase in GFR. In term neonates, GFR increases rapidly over the 1st few months of life and approaches adult values by 10-12 mo of life (see Fig. 60-3D). The rate of GFR acquisition is blunted in preterm neonates consequent to continued nephrogenesis, which occurs in the early postnatal period. In young children between 2 and 5 yr of age, GFR may exceed adult values, especially during periods of increased metabolic demand (e.g., during a fever).

In addition, there is a relative glomerular/tubular imbalance because of a more advanced maturation of glomerular function. Such an imbalance may persist up to 6 mo of age and may account for the observed decrease in the ATS of drugs commonly used in neonates and young infants (e.g., β-lactam antibiotics). Finally, there is some evidence that ATR is reduced in neonates and that it appears to mature at a slower rate than the GFR.

Altered renal drug clearance in the newborn and infants result in the different dosing recommendations commonly seen in pediatrics. The aminoglycoside antibiotic gentamicin provides an illustrative example. In adolescents and young adults with normal values for GFR (85-130 mL/min/1.73 m²), the recommended dosing interval for the drug is 8 hr. In young children who may have a GFR >130 mL/min/1.73 m², a gentamicin dosing interval of every 6 hr may be necessary in selected patients who have serious infections that require maintaining steady-state peak and trough plasma concentrations near the upper boundary of the recommended therapeutic range. In contrast, to maintain “therapeutic” gentamicin plasma concentrations in neonates during the 1st few weeks of life, a dosing interval of 18-24 hr is required.

The impact of developmental differences in GFR on the elimination characteristics of a given drug can be assessed by estimating the apparent elimination rate constant (Kel) for a drug by using the following equation:

\[
\text{Kel (in reduced renal function)} = \frac{\text{Kel}_{\text{normal}} \cdot (\text{GFR}_{\text{observed}} / \text{GFR}_{\text{normal}} - 1) \cdot \text{Fel}}{1 + \text{Fel}}
\]

where the \(\text{Fel}\) represents the fraction of the drug excreted unchanged in an adult with normal renal function, \(\text{GFR}_{\text{observed}}\) is the value calculated (from creatinine clearance or an age-appropriate estimation equation) for the patient (in mL/min/1.73 m²), \(\text{GFR}_{\text{normal}}\) is the average value considered for a healthy adult (i.e., 120 mL/min/1.73 m²) and \(\text{Kel}_{\text{normal}}\) is estimated from the average elimination \(T_\text{1/2}\) (terminal half-life) for a drug taken from the medical literature using the following equation:

\[
\text{Kel}_{\text{normal}} [\text{hr}^{-1}] = 0.693 / T_{1/2}\text{normal} [\text{hr}]
\]
Likewise, the elimination $T_e$ for a drug in patients with reduced renal function can be estimated as follows:

$$T_e \text{ (in reduced renal function)} = 0.693/Ke \text{ (in reduced function)}$$

An estimate of the drug elimination $T_e$ in patients with reduced renal function with knowledge of the desired interdose excursion in steady-state plasma concentrations can provide an ability to determine the desired drug dosing interval.

**Impact of Ontogeny on Pharmacodynamics**

Although, it is generally accepted that developmental differences in drug action exist, there is little evidence of true age-related pharmacodynamic variation among children of differing age groups and adults. Drug action is typically mediated by interaction of a small molecule with 1 or more receptors, which may be located either on or in a cell. Drug effect is mediated at the receptor by 4 main biochemical mechanisms involved in cell signaling. Binding of the receptors on the cell surface or within the cell activate downstream pathways that mediate a specific cellular action. Some receptors act as enzymes whereby, upon ligand binding, the enzyme phosphorylates downstream effector proteins, thereby activating or inhibiting a cellular signal. Guanosine triphosphate–binding regulatory protein, also known as G-protein–coupled receptors, are known targets for many drugs. Upon ligand binding, guanosine triphosphate binds to and activates the G-protein, in turn allowing it to activate second messenger regulatory proteins in the cell, again mediating cellular signaling. Other receptors mediate their actions through ion channels whereby, upon ligand binding, the cell’s membrane potential or ionic composition is altered allowing cellular activation or inhibition. Lastly, some receptors act as transcription factors that, when bound by a ligand, transcription of specific genes within the cell are activated. Drug action is concentration dependent with onset and offset generally associated with appearance and disappearance, respectively, of the drug at the receptor(s) in an amount that is sufficient to initiate the cascade of biologic effects that terminate in drug action (see Fig. 60-1). The minimum effective concentration of a drug is that observed with the immediate onset of effect, whereas the duration of action is predicated upon the maintenance of drug concentrations at the receptor within a range that is associated with the desirable pharmacologic action(s). Receptor binding by a drug may have varying consequences. Drugs that are agonists bind to and activate the receptor, directly or indirectly achieving the desired effect. An agonist binding to a receptor results in the same biologic effect as binding of the endogenous ligand. Partial agonists bind to a receptor in activation of the receptor but maximal effect is not achieved even in the presence of receptor saturation. Antagonists bind to a receptor preventing binding of other molecules thereby preventing activation of the receptor.

Age-related pharmacokinetic variation resulting in altered drug disposition may result in less or more drug being available at the receptor(s) consequent to whether drug clearance is decreased or increased relative to values in adults. The resultant alteration in the dose–concentration profile may result in an attenuated (ineffective) or exaggerated (toxicity) response in children, which is especially relevant for drugs with a narrow therapeutic index (Fig. 60-4). Thus, in some circumstances, apparent developmental differences in drug response/ effect may be simply explained on pharmacokinetic basis.

There is evidence supporting developmental differences in receptor number, density, distribution, function, and ligand affinity for some drugs. As there are limited data from humans, much of what is known has been derived from animal studies. In the CNS, unique developmental aspects of drug–receptor interaction affect therapeutic efficacy of both analgesic and sedative drugs in neonates. For example, the number of γ-aminobutyric acid receptors, which mediates inhibitory signal transduction in the CNS, is reduced in newborns compared to adults. Functional differences have also been observed between neonatal and adult brain upon γ-aminobutyric acid receptor activation. These changes may explain observed differences in dosing of drugs such as midazolam in infants, and in part may explain seizures experienced by infants upon benzodiazepine exposure. Another example in the CNS is illustrated by the μ-opioid receptor whereby receptor number is reduced in newborns and receptor distribution also differs between newborns and adults.

For the clinician, the consideration of age-dependent differences in pharmacodynamics is particularly relevant when they are associated with adverse drug reactions (e.g., higher incidence of valproic acid-associated hepatotoxicity in young infants; greater frequency of paradoxical CNS reactions to diphenhydramine in infants; weight gain associated with use of atypical antipsychotic drugs in adolescents) or when drugs have a narrow therapeutic index. This latter situation is exemplified by the immunomodulatory agent cyclosporine and the anticoagulant warfarin. In children younger than 1 yr old, the mean concentration of cyclosporine required to inhibit monocyte proliferation and the expression of the inflammatory cytokine interleukin-2 is less than required in older children. The age-associated pharmacodynamics of warfarin observed in children with congenital heart disease is, to a great degree, associated with developmental differences in serum concentrations of vitamin-K dependent coagulation factors (II, VII, IX, X) between children and adults. Developmental differences in drug action have also been observed between prepubertal children and adults with regard to warfarin action. Prepubertal children compared to adults exhibit a more profound response, demonstrated by lower protein C concentration, prothrombin fragments 1 and 2, and greater rise in international normalized ratio, to comparable doses of warfarin. Thus, when age-dependent pharmacodynamics of a given drug are evident, the use of simple allometric approaches for “scaling” the pediatric dose from the usual adult dose may not produce the desired pharmacologic effects.

**Surrogate End Points**

The assessment of pharmacodynamics in human infants and children has been hampered historically by a relative inability to use invasive methods for the direct assessment of drug effect. As a result, surrogate end points and biomarkers have been explored and, in some cases, have been successfully used to evaluate the impact of ontogeny on pharmacodynamics.

Biomarkers and surrogate end points (markers) are ideally simple, reliable, inexpensive, and easily obtainable measures of a biologic response or disease phenotype that can be used to facilitate either clinical research or patient care. Biomarkers have been defined by the U.S. National Institutes of Health as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.” A surrogative end point is defined “as a biomarker that is intended to substitute for a specific clinical end point. A surrogate end point is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or...
other scientific evidence.” Reliable surrogate end points predict a specific physiologic event(s) (e.g., intraesophageal pH to assess gastroesophageal reflux), which may be utilized diagnostically, prognostically, or in predicting a specific drug response (therapeutic, subtherapeutic, or adverse) or potentially, the impact of ontogeny on pharmacodynamics. Specific examples of surrogate end points used in pediatric pharmacology include measurement of esophageal pH to assess the action of prokinetic or acid-modifying drugs, use of gastric scintigraphy and stable isotope-labeled compounds (e.g., 13C-acetate, 13C-octanoic acid) to assess gastric emptying rate, and pulmonary function tests (e.g., forced expiratory volume at 1 sec) to evaluate the effect(s) of drugs on pulmonary function in patients with conditions such as asthma and cystic fibrosis. Examples of biomarkers that have been used in pediatric studies to assess drug disposition or effect include hemoglobin A1c, plasma concentration (to assess efficacy of peroral hypoglycemic agents); urinary leukotriene concentrations (to assess effects of nonsteroidal antiinflammatory drugs); minimal inhibitory and minimal bactericidal concentrations of drugs to selected antiinfective agents; and the use of selective genotyping tests (e.g., projection of therapeutic warfarin dose requirement by use of CYP2C9 [gene controlling expression of the enzyme primarily responsible for warfarin metabolism] and VKORC1 [gene controlling expression of enzyme primarily involved in regulating warfarin effects on vitamin K dependent clotting factors] genotyping.

**Additional Considerations in Pediatric Therapeutics**

The use of adult-dose modification for pediatric dose prediction is based on the association between body size/composition and the physiologic determinants of drug disposition across the spectrum of age. Although these approaches may have some potential clinical utility in children older than 8 yr of age and in adolescents whose organ function and body composition approximates that of young adults, their utility is severely limited in neonates, infants, and children younger than 2 yr of age in whom ontogeny produces dramatic differences in drug disposition. This is especially problematic for therapeutic drugs whose doses cannot be easily individualized using patient-specific pharmacokinetic data obtained from therapeutic drug monitoring.

More than 20 different approaches for initial selection of a drug dose for pediatric patients have been described. The majority of these utilize either total body weight (BW) or body surface area (BSA) as surrogates, which reflect the developmental changes of either body composition or organ function that collectively are the major determinants of drug disposition. Dose selection based on BW or BSA will generally produce similar relationships between drug dose and resultant plasma concentration, except for those drugs whose apparent VD corresponds to the extracellular fluid pool (i.e., VD < 0.3 L/kg) for which a BSA-based approach is preferable. In contrast, for drugs whose apparent VD exceeds the extracellular fluid space (i.e., VD ≥ 0.3 L/kg), a BW-based approach for dose selection is preferable, which is the most frequently used method in pediatrics. When the pediatric dose for a given drug is not known, these principles can be used to best approximate a proper dose for the initiation of treatment as is illustrated by the following equations:

- Child dose (if VD < 0.3 L/kg) = (child BSA in m²/1.73 m²) × adult dose
- Infant dose (if VD ≥ 0.3 L/kg) = (infant BW in kg/70 kg) × adult dose

It should be noted that this approach assumes that the child’s weight, height, and body composition are age appropriate and normal, and that the “reference” normal adult has a BW and BSA of 70 kg and 1.73 m², respectively. It is useful only for selection of dose size and does not offer information regarding dosing interval because the equations contain no specific variable that describes potential age-associated differences in drug clearance.

In neonates and young infants with developmental immaturity in either GFR and/or ATS, it is often necessary to adjust the “normal” dosing interval (i.e., that used for older infants and children who have attained developmental competence of renal function) for drugs with significant (>50%) renal elimination so as to prevent excessive drug accumulation and possible associated toxicity with administration of multiple doses. To accomplish this therapeutic goal, it is necessary to estimate the apparent T1/2 of the drug.

**Drug-Level Monitoring**

Drug response (either therapeutic or toxic) occurs only as a consequence of drug exposure. Clinically, systemic drug exposure is most commonly evaluated through assessing the plasma drug concentration; a surrogate measurement for a drug reaching its pharmacologic receptor(s).

In the patient, drug-level monitoring can be used to facilitate 2 approaches for evaluating the dose–concentration–effect relationship; therapeutic drug monitoring and pharmacokinetic-based dose individualization (clinical pharmacokinetics). **Therapeutic drug monitoring** largely entails a retrospective, reactive approach whereby drug concentrations in plasma (primarily) or other biologic fluids are measured at some point during either a constant rate intravenous infusion or during a dosing interval for drugs given by intermittent dosing schedules. These levels are then compared with those that are “desired” for a given drug based on published information and used to adjust the dose/dosing regimen in a quasi-empiric fashion. In using a therapeutic drug-monitoring approach, it should be recognized that for many drugs that are therapeutically monitored in the clinical setting (e.g., aminoglycoside antibiotics, vancomycin, phenytoin, phenobarbital, cyclosporine, tacrolimus, mycophenolate mofetil, selected antiretroviral drugs, acyclovir), “desired” plasma concentrations are generally determined from studies in adult patients in whom drug disposition and disease states may be quite different from those in infants and children.

In contrast to therapeutic drug monitoring, **clinical pharmacokinetics** represents a prospective, proactive approach where plasma drug concentrations are used to estimate pharmacokinetic parameters (e.g., apparent Kel, elimination T1/2, apparent VD, total plasma clearance, AUC) which are then used to calculate a dosing regimen required to attain a desired level of systemic exposure (e.g., AUC, steady-state peak and/or trough plasma drug concentrations) that would portend a desired pharmacologic response. Of these 2 approaches, the use of drug-level data for performing clinical pharmacokinetics provides the most optimal approach for individualizing dose/dosing regimen and maintaining some adaptive control over the dose-concentration–effect relationship. This approach is particularly useful for patients who by virtue of their age and/or disease states, may have “abnormal” pharmacokinetics. Approaches used to enable the performance of clinical pharmacokinetics include the manual use of established formulas for calculating pharmacokinetic parameters (generally using a simple 1 compartment open model consequent to the few number of plasma drug-level observations obtained in the context of clinical patient care) or computer-based algorithms (e.g., Bayesian estimation, population-based pharmacokinetic approaches).

Common to both of the aforementioned approaches is the need to accurately assess plasma drug concentrations in a given patient. Figure 60-5 represents a hypothetical general steady-state plasma concentration vs time profile for a drug given by an extravascular route. It is provided to illustrate the following general principles that should be recognized and/or followed when plasma drug-level monitoring is used in patients as a “tool” to individualize drug treatment:

- When a drug reaches a pharmacokinetic steady state (a period corresponding to 5 times the apparent elimination Te/2 for a given drug), both the excursion between the peak (Cmax) and trough (Cmin) plasma concentration and the AUC are identical between dose intervals provided that (1) the dose is not changed; (2) an exact dose-to-dose interval is maintained for drug administration; and (3) the route or rate of drug administration between dosing intervals has not changed.
- Steady-state plasma drug concentrations provide the best surrogate for assessing exposure–response relationships for a given drug.

When used to support clinical pharmacokinetic approaches for dose regimen design, they provide the most accurate estimation of patient-specific pharmacokinetic parameters. Plasma
Drug Formulation and Administration
One of the more unique challenges in pediatric therapeutics is the drug formulation itself. Despite the increasing sensitivity for the need to study drugs in children before they are used in children and to have available “pediatric-friendly” formulations, many drug products that are formulated only for use in adults are routinely given to pediatric patients. Their use can result in inaccurate dosing (e.g., administration of a fixed dose to children with widely varying body weights), loss of desired performance characteristics of the formulation (e.g., crushing a sustained-release tablet or cutting a transdermal patch) and the exposure of infants and children to excipients (e.g., binding agents, preservatives) in amounts capable of producing adverse effects.

Peroral Drug Administration
One of the principal determinants of peroral drug administration in children is the ability to actually get the drug into the body. Peroral formulations are often expelled by children because of poor taste and texture. This is a significant issue, especially when considering that taste sensation differs as a consequence of development and on an interindividual basis. Solid formulations, such as tablets and capsules, are not easily administered to the majority of infants and children owing to their inability to easily and safely swallow them. For example, incomplete development of swallowing coordination may result in choking or aspiration when solid formulations are given to infants and small children. Finally, solid peroral formulations limit the ability for dose titration and dosing flexibility. Drug developers in the United States and abroad are working to address this limitation by the development of new techniques suitable for both oral and peroral drug administration that encompass both products (e.g., dispersible peroral tablets, oral films, titratable granules, oral melts) and drug administration devices (e.g., dosing straws, graduated cylinders for peroral granules).

With regard to dosing accuracy with peroral formulations, liquids (e.g., drops, solutions, syrups, suspensions, elixirs) are preferred for infants and young children. The utility of these formulations is often limited by palatability when taste-masking of the active ingredient(s) cannot be effectively achieved. In the case of suspension formulations, improper reconstitution and/or resuspension prior to dose administration can introduce problems related to accuracy of dosing. Other potential limitations of peroral liquid drug formulations (including those that may be extemporaneously compounded by the pharmacist from drug powder or from solid peroral dosage forms of a given drug) include potential problems related to drug stability, contamination (chemical or bacterial), portability and for some products, the need for them to be refrigerated so as to insure drug stability.

Administration of liquid medications can be associated with risk if the device for administering the medication is not appropriate (e.g., use of a kitchen teaspoon as opposed to a 5.0 mL dosing spoon) or used improperly when measuring a dose that is appropriate for the patient’s age or weight. The low cost and convenience of hypodermic syringes has prompted many physicians and pharmacists to dispense them with liquid medications in order to improve accuracy. Although this approach is seemingly associated with greater accuracy in dosing, parents/caregivers can have difficulty in reading the graduations on a syringe and, also, the plastic caps on the plungers of syringes can produce a choking hazard for infants and young children. All of these problems can be obviated by education of parents/caregivers on how to reliably use special syringes for peroral dosing that pharmacists should dispense with every liquid drug formulation.

Parenteral Drug Administration
In contrast to adults where vascular access is relatively easy to obtain, difficulties are often present in the infant and young child. These are often produced by the smaller diameter of peripheral vessels (relative to the size of the intravenous cannula), developmentally associated differences in body composition (e.g., body fat distribution) and the use of topical anesthetic agents, some of which can produce venous constriction. The small peripheral blood vessels in infants and young children can also limit the volume and rate of intravenous drug administration because of issues of capacity and, in the instance of drugs capable of producing venous irritation, infusion-related discomfort.

An underappreciated issue that can complicate parenteral drug administration to infants occurs when the concentration of a given drug formulation does not enable accurate measurement of dose. Errors consequent to improper dilution of adult formulations necessary to ensure appropriate osmolality and volume for IV administration (the most common resulting in a 10-fold overdose) are not uncommon. For example, morphine, a drug commonly used in neonates, infants, and children, is commonly available in a 2 mg/mL...
concentration. A usual 0.1 mg/kg morphine dose for a 1 kg infant using this formulation would require a nurse or pharmacist to accurately withdraw 0.05 mL and administer it into a length of IV tubing with a dead space volume that may exceed that of the dose by approximately 100-fold. In this situation, accuracy of dose and infusion time can be significantly compromised. Although underdosing is often a serious problem when attempting to administer very small volumes, overdoses also occur, owing to inaccurate extemporaneous dilutions. Moreover, attempts to compensate for the volumes present within the IV tubing further predispose the patient to receive an incorrect, possibly unsafe, dose. Whenever such concentrated drug formulations are the only source for use, appropriate alteration of the stock parenteral solution should be performed and manufactured by the pharmacy department. As well, many errors can be avoided by the use of standard dilutions that all practitioners are aware of and using standardized approaches for IV drug administration that minimize complications associated with unrealized drug dilution and errant infusion times (e.g., pediatric syringe pumps attached to low-volume tubing).

Although used rather infrequently, IM drug administration offers a route of administration for many drugs in those instances where venous access is not immediately available or when a therapeutic drug regimen involves use of a single or limited number of doses. Although appealing with respect to immediacy, this route of administration can be associated with problems (e.g., muscle and/or nerve damage, sterile abscess formation, variable rate of drug absorption consequent to developmental differences in vascular perfusion of muscle beds), especially in the neonate and small infant. Finally, the decision to utilize the IM route must take into consideration the physicochemical properties (e.g., pH, osmolarity, solubility) of the drug formulation and/or any diluent used to prepare it.

Other Routes for Drug Administration
Neonates, infants, children, and adolescents with certain pulmonary conditions (e.g., reactive airway disease, viral-induced bronchiolitis, asthma, cystic fibrosis) frequently receive drugs (e.g., corticosteroids, β-adrenergic agonists, antimicrobial agents, mucolytic drugs) via inhalation. The pulmonary surface area in pediatric patients of all ages is a very effective, easily traversable barrier for drug absorption. Rate-limiting factors for pulmonary drug absorption include physicochemical factors associated with the drug and delivery system (e.g., particle size, diffusion coefficient, chemical stability of drug molecule in the lung) and physical factors that influence intrapulmonary drug deposition (e.g., active vs passive drug delivery to the tracheobronchial tree, respiratory minute volume, internal airway diameter); many of which are developmentally determined. For drugs formulated for delivery using a metered-dose inhaler (either drug powder or suspended particles using a carrier gas), developmental factors (e.g., incoordination of device actuation with inhalation, inability to follow instructions for clearing of airway, and passive inhalation with actuation of delivery device) either prevent their use (such as in infants and small children) or limit the bioavailability of the drug to be administered. In these instances, specific devices (e.g., masks, spacer chambers) and/or methods of delivery (e.g., continuous aerosolization via mask) can be used to improve the efficiency of drug delivery and, thereby, drug efficacy.

In pediatric patients, percutaneous drug administration is generally reserved for agents intended to produce a local effect within the dermis. Development has an impact on the barrier of the skin that, if not recognized and controlled for, can produce situations in which systemic toxicity can result (see “Drug Absorption” above). Similar therapeutic challenges occur when transmucosal routes (e.g., buccal, sublingual, rectal) are used for drug administration. Specifically, unpredictable systemic bioavailability may complicate treatment consequent to variability in the rate and/or extent of drug absorption. Finally, direct intraosseous drug administration via puncture of the tibia is occasionally used in infants and small children for administration of drugs and crystalloid fluids given acutely during resuscitation efforts. It is particularly useful when vascular access sufficient for drug administration cannot be immediately accomplished as the onset of action by this route is comparable with that seen after IV administration.

Adherence and Compliance
Beyond proper individualization of drug dose based on developmental considerations, the influence of concomitant disease/treatment and the selection of the proper drug formulation, the success of drug treatment in a pediatric patient is inextricably linked to the successful administration of the drug. Physical and cognitive immaturity makes the infant and the child a dependent creature in almost all respects, including those related to therapeutic drug administration. Until a child reaches an age at which they can physically self-administer a drug in an accurate, proficient fashion and can mentally assume responsibility for this task (generally from 7-14 yr of age, depending on the individual child), compliance with a drug regimen becomes the responsibility of an adult. In a hospital environment, compliance is ensured through the actions of physicians, nurses, and pharmacists who, collectively through an integrated system of medical care, assume this responsibility. Upon discharge, the responsibility is transferred to parents/guardians or other adult caregivers in an environment that is generally nonmedical. At this juncture, therapeutic compliance morphs into adherence as defined by the potential for conflicting demands (e.g., multiple adult caregivers; different external environments such as home, daycare, school; parents tending to the needs of multiple children) to introduce variability (anticipated and unpredictable) in drug administration. Whether treatment is for a self-limiting (e.g., antibiotic administration) or chronic (e.g., asthma, diabetes) condition, challenges to therapeutic adherence have the potential to serve as primary determinants of drug safety and efficacy in infants and young children.

In contrast to the period encompassing infancy and childhood, adolescence poses its own unique challenges to therapeutic adherence. During this period, psychosocial maturation almost always lags behind physical maturation. Development of cognitive and physical skills in most adolescents enables them to self-administer a prescribed medication in a proper manner with little to no supervision. However, psychodynamic issues experienced by a substantial number of adolescents (e.g., complete understanding of the ramifications of undertreatment, disease progression, and/or roles of disease prevention, and/or health maintenance; perceptions of immortality and the associated lack of need for treatment; disorganized patterns of thinking capable of confounding treatment schedules; defiant/oppositional behavior toward authority figures) can often precipitate therapeutic failure, through either undertreatment or overtreatment, the latter occasionally leading to drug toxicity. Unfortunately, the only maneuver that can be used to facilitate therapeutic compliance and adherence in the pediatric patient is the combination of vigilance (on behalf of all caregivers) and repetitive education coupled with positive reinforcement (e.g., the use of motivational interviewing techniques). When children reach the age of consent (i.e., generally by 7 yr of age in children who have normal neurobehavioral development), they have the beginning level of cognitive ability sufficient to engender understanding about their medical condition(s) and how effective treatment can be used to improve their life. Through diligent efforts placed toward patient education and reeducation, older children and adolescents can assume a level of responsibility for active partnership in their overall medical management, one that will mature as educational efforts, driven by a shared desire for an optimal outcome, are regularly made. The pediatrician’s role in fostering this is paramount given their understanding of development and the regular patient–parent interactions that occur from birth through adolescence.

Drug–Drug Interactions
Pharmacokinetic and/or pharmacodynamic properties of drugs may be altered when 2 or more drugs are coadministered to a patient (refer to Table 60-6). Even though many interactions occur at the level of drug metabolism, they may also occur at the level of drug absorption (e.g., inhibition of intestinal CYP3A4 activity by grapefruit juice or St. John’s wort) and consequent reduction in presystemic clearance of
CYP3A4 substrates), distribution (e.g., displacement of warfarin plasma protein binding by ibuprofen with consequent increased hemorrhagic risk), or elimination (e.g., inhibition of ATS of β-lactam antibiotics by probenecid). Drug–drug interactions may also occur at the level of the receptor (via competitive antagonism), many of which are intentional and produce therapeutic benefit in pediatric patients (e.g., antihistamine reversal of histamine effects, many of which are predictable based on a priori knowledge of a given drug's biotransformation profile). Although such information can be derived from the primary literature, it may not be immediately translated into a useful clinical context consequent to limitations associated with in vitro to in vivo extrapolation, which can (1) use of animal models for characterizing metabolism; (2) extrapolating enzyme kinetics derived from pooled human liver microsomes or recombinant human drug-metabolizing enzymes to estimates of in vivo drug clearance; (3) extrapolating in vitro data obtained from fully competent (i.e., adult activity) hepatic microsomes to estimates of clearance in patients who may have developmental and/or disease-associated compromise in enzyme activity; (4) inaccurate accounting for pharmacogenetic variation in drug-metabolizing activity (i.e., constitutive activity); (5) the contribution of multiple different drug-metabolizing enzymes in the overall biotransformation of a given drug (i.e., a polyfunctional drug substrate); (6) the potential role of enzyme induction or inhibition in vivo that is not reflected from conditions used for in vitro metabolism studies.

Despite these limitations, information pertaining to drug–substrate interaction can be useful in ascertaining the direction (e.g., enzyme inhibition → reduced clearance → higher plasma drug concentration → enhanced effect as compared to enzyme induction → increased clearance → reduced plasma drug concentration → diminished effect) of a drug–drug interaction. Although multiple sources describing specific drug–drug interactions exist (e.g., primary and secondary literature, drug product labeling), the information may not be complete or updated. In examining multiple information sources pertaining to this topic, the authors found a data compilation from Indiana University (http://medicine.iupui.edu/clinpharm/ddis/) to be the most complete and clinically useful. Utilizing primary literature should be assessed when information is not available in online sources.

Drug interactions may also occur at a pharmaceutical level as a result of a physicochemical incompatibility of two medications when combined. Such interactions generally alter the chemical structure of 1 or both constituents, thereby rendering them inactive and potentially dangerous (e.g., intravenous infusion of a crystalline precipitate or unstable suspension). For example, ceftriaxone should be avoided in infants younger than 28 days of age if they are receiving or are expected to receive intravenous calcium-containing products because of reports of neonatal deaths resulting from crystalline deposits in the lungs and kidneys. Alternatively, 2 drugs simultaneously administered perorally may form a complex that can inhibit drug absorption (e.g., coadministration of doxycycline with a food or drugs containing divalent cations).

Nonprescription preparations, herbal supplements, and certain foods also have the potential to produce interactions with drugs. These are often quite challenging for the clinician, especially for alternative therapies, in that their composition (or potency) may not be completely discernable from the product labels and because the disposition of many natural products has not been studied in either children or adults. Many patients and their parents also do not consider alternative

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**Table 60-6 Mechanism-Based Drug Interaction Table**

<table>
<thead>
<tr>
<th>PHARMACODYNAMIC</th>
<th>EXAMPLE DRUG COMBINATION</th>
<th>RESULT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additive</td>
<td>a. Fentanyl and midazolam</td>
<td>Use of multiple medications with similar side effect profiles can lead to additive effects such as increased sedation (a), increased QT prolongation (b), and increased potential for nephrotoxicity (c).</td>
</tr>
<tr>
<td></td>
<td>b. Class IA antiarrhythmic with erythromycin</td>
<td>Improved bactericidal efficacy against some Gram-positive organisms.</td>
</tr>
<tr>
<td></td>
<td>c. Vancomycin plus aminoglycoside</td>
<td>Use of penicillin inhibits bacterial cell wall synthesis which for some Gram-positive organisms can improve the intracellular penetration of the aminoglycoside, which inhibits bacterial cell protein synthesis by binding to 30S and 50S ribosomal subunits</td>
</tr>
<tr>
<td>Synergy</td>
<td>Penicillin plus aminoglycoside</td>
<td>Competitive receptor antagonism: Decreased efficacy of opiate medications, improvement in respiratory effort</td>
</tr>
<tr>
<td>Antagonism</td>
<td>Opiate plus naloxone</td>
<td></td>
</tr>
</tbody>
</table>

**PHARMACOKINETIC**

- **Absorption**
  - *Inhibition of MDR1*: Amiodarone and digoxin
    - *Complex formation*: Quinolone and tetracycline antibiotics with divalent/trivalent cations (e.g., Ca²⁺, Mg²⁺, Fe³⁺, Al³⁺)
    - Mycophenolate mofetil plus antacids
    - *Pharmaceutical preparations*: Ceftriaxone with IV fluids containing calcium
  - *Distribution*: Ceftriaxone + endogenous bilirubin
    - NSAID plus warfarin
  - *Metabolism*:
    - *Induction*: Rifampin plus antiretrovirals
    - *Inhibition*: Azole antifungals plus CYP3A4 substrates
  - *Elimination*: Penicillin plus probenecid
    - Methotrexate plus aspirin

- **Increased digoxin concentration, digoxin toxicity (↓ digoxin 50%)**
- **Decreased antibiotic absorption**
- **Decreased absorption of mycophenolate mofetil**
- **Crystalline deposits in lungs/kidneys of neonates**
- **Displacement of bilirubin from albumin binding site, increased risk kernicterus in neonates**
- **Displacement of warfarin from albumin binding site with consequent exaggerated anticoagulant response**
- ** Decreased serum concentration of antiretroviral because of induced CYP metabolism**
- **↑ Drug levels because of inhibition of CYP3A4-mediated metabolism resulting in drug toxicity**
- **Decreased tubular secretion of penicillin resulting in increased serum concentrations**
- **Inhibition of renal tubular secretion of methotrexate resulting increased methotrexate concentration**

This table is not meant to be an all-inclusive list of drug–drug interactions. Care should be taken when prescribing all medications, and the potential of interactions should be considered. The practitioner is encouraged to assess the possibility of all interactions when prescribing medications.

NSAID, nonsteroidal antiinflammatory drug.

Adverse Drug Reactions

Adverse drug reactions (ADRs) have been defined by the World Health Organization as “a response to a drug that is noxious and unintended, and occurs at doses normally used for the prophylaxis, diagnosis, therapy or treatment of disease or for the modification of physiological functions.” There are 2 traditional pharmacologic classifications of ADRs: type A and type B. Type A reactions are dose dependent, predictable, and account for 85-90% of all ADRs. These are often considered as “side effects” to medications. Type B reactions are not dose dependent, are unpredictable and account for approximately 10-15% of all adverse reactions. These are generally considered to represent hypersensitivity (i.e., allergic) reactions whereas some can have a non-immune basis. Historically, such standardized definitions describing adverse events have not been routinely utilized. Furthermore, patients sometimes misinterpret some side effects as allergies (e.g., diarrhea with amoxicillin/clavulanate) and this may be perpetuated through the patient’s medical record, thus potentially restricting a useful and necessary medication.

In the pediatric population, ADRs are common occurrences that produce a major burden to patients and the healthcare system. Studies concerning ADRs in pediatric patients suggest the following: (1) approximately 9% of all pediatric patients admitted to the hospital experience an ADR during their treatment; (2) the apparent incidence of ADRs in children in outpatient clinics is approximately 1.5%; (3) ADRs have been reported as being responsible for >2% of pediatric admissions to children's hospitals; and (4) approximately 40% of ADRs occurring in hospitalized children are potentially life-threatening. In considering these “statistics” it should be recognized that the true incidence of ADRs in children is not known as a consequence of generalized underreporting by healthcare providers (physicians, nurses, pharmacists), parents/caregivers, and patients (who may not recognize signs/symptoms and/or be unable to report them), and in many countries (including the United States), the lack of a standardized surveillance and real-time reporting system. As a consequence, estimation of their incidence relies upon spontaneous, volunteer reporting systems that lack uniformity and critical evaluation and do not provide both numerator and denominator data necessary to determine true incidence of a specific ADR in a specific subpopulation of patients.

Despite the limitations associated with determining the incidence of ADRs in children, it is estimated that their occurrence in patients 0-4 yr of age (3.8%) is more than double that seen at any other time throughout childhood and adolescence. The reasons for this are not currently known but may involve developmental differences in pharmacokinetics and/or pharmacodynamics (i.e., altered dose-concentration–effect relationship), age-associated differences in physiologic “systems” that modulate drug and/or metabolite-mediated cellular injury (e.g., the immune system) and/or the therapeutic use of drugs known to have a relatively high incidence of producing ADRs (e.g., delayed hypersensitivity reactions associated with β-lactam antibiotics). Also, it is important to recognize that infants can experience ADRs from drugs that are not administered to them therapeutically, but from incidental drug exposure (e.g., transplacental drug passage, breastfeeding). Examples include neonatal abstinence syndrome associated with maternal opiate use, production of a hyperserotonergic state in neonates born to mothers who received selective serotonin reuptake inhibitors during and through pregnancy, and opiate toxicity in breastfed infants whose mothers were taking codeine for pain management. In these instances, drug accumulation occurring because of reduced activity of drug-metabolizing enzymes associated with development, and, potentially, pharmacogenetically determined phenotypic changes that, in concert, can produce a level of systemic drug exposure sufficient to produce exaggerated drug response or frank toxicity.

There are also specific ADRs that occur at a much greater frequency in infants and children as compared to adults. Examples include aspirin-associated Reye syndrome, cefaclor-associated serum sickness-like reactions, lamotrigine-induced cutaneous toxicity, and in infants younger than 2 yr of age, valproic acid–induced hepatotoxicity. It is not clear whether the age prediction for these specific ADRs is associated with developmental differences in drug biotransformation related to both metabolite formation and detoxification or, alternatively, has a pharmacogenetic basis. Finally, it should be recognized that children, like adults, do experience hypersensitivity reactions to drugs. Examples include reactions to anticonvulsant drugs (e.g., phenytoin, carbamazepine, valproate), sulfonamides (e.g., sulfamethoxazole, sulfadiazine), minocycline, cefaclor, and abacavir. These specific ADRs are not characteristic of type I (i.e., immediate) hypersensitivity reactions (e.g., true penicillin allergy) or anaphylactoid reactions; rather, they represent delayed hypersensitivity reactions that are classified as idiosyncratic with respect to their origin. A relatively common constellation of symptoms (fever, rash, and lymphadenopathy) suggests that abnormal activation/regulation of the immune system is a predominant component of their pathogenesis. Data from in vitro studies of sulfamethoxazole hypersensitivity also support this assertion. A requisite role for metabolic bioactivation (for anticonvulsants, sulfamethoxazole, and cefaclor) and, possibly, genetic factors, such as allelic variants in HLA-B (e.g., HLA-B*5701 and HLA-B*1502 associated with hyper-sensitivity reactions to abacavir and carbamazepine) appear also to be involved in their etiology.

PERSONALIZED MEDICINE

See also Chapter 59.

The general concept of personalized medicine involves the application of genomic information to predicting a disease, disease severity, and therapeutic response. This “new vision of medicine” has been described as the 3 Ps: predictive, personalized, and preventive. However, in children, ontogeny should also be considering when
discussing personalizing therapeutic treatments. Thus, the aim of pediatric personalized medicine is to uniquely combine genetic variation with developmental stage to provide a tailored approach to either drug avoidance (in the case of predicted, significant risk of an ADR) or treatment.

*Bibliography is available at Expert Consult.*
Bibliography


The primary purpose of general anesthesia is to suppress the conscious perception of, and physiologic response to, noxious stimuli and to render the patient unconscious. Potent drugs are used to blunt physiologic responses to what would otherwise be life-threatening trauma (surgery). Intraoperatively, the anesthesiologist is responsible for providing analgesia as well as physiologic and metabolic stability (Table 61-1). This responsibility is facilitated by obtaining an adequate preanesthesia history (Table 61-2). Although anesthetic risk has greatly decreased, the increased risk of morbidity and mortality in the perioperative period demands the utmost vigilance. The risk is even higher in certain disease states (Table 61-3).

### GENERAL ANESTHESIA

**Analgesia**

Providing analgesia for procedures both in and out of the operating room is a major responsibility and function within a spectrum of care (Table 61-4). Techniques exist to provide profound pain relief during operative procedures for all patients, including the most critically ill infants. Blunting the physiologic responses to painful stimuli inhibits the stress response and its multiple deleterious physiologic and metabolic consequences. The response to painful and stressful stimuli is a potent stimulus of the systemic inflammatory response syndrome, which leads to increased catabolism, physiologic instability, and increased mortality (see Chapter 70). Appropriate use of medication, such as fentanyl anesthesia in neonates, reduces the incidence of postoperative bradycardia, hypotension, acidosis, intraventricular hemorrhage, coagulation abnormalities, hypoglycemia, and death.

**Hypnosis and Amnesia**

The blunting of both consciousness (hypnosis) and conscious recall (amnesia) is a crucial feature of pediatric anesthesia care. Awareness of painful, anxiety-provoking, and stressful conditions for children is

<table>
<thead>
<tr>
<th>Table 61-1</th>
<th>Goals of Anesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesia</td>
<td>Amnesia and a decreased level of consciousness</td>
</tr>
<tr>
<td></td>
<td>Akinesia—absence of movement in response to painful stimuli</td>
</tr>
<tr>
<td></td>
<td>Physiologic support and homeostatic management throughout the perioperative process</td>
</tr>
<tr>
<td></td>
<td>Vigilance</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 61-2</th>
<th>The Preanesthetic History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child’s previous anesthetic and surgical procedures:</td>
<td></td>
</tr>
<tr>
<td>• Review the anesthetic record for information about the mask and endotracheal tube size; the type and size of laryngoscope used; difficulties with mask ventilation or intubation; prolonged emergence (awakening) from anesthesia; postoperative vomiting, postoperative agitation and disordered postoperative behavior in the days following anesthesia/surgery. In addition, a history of hyperthermia or acidosis in the child or family member should be sought.</td>
<td></td>
</tr>
<tr>
<td>Perinatal problems (especially for infants):</td>
<td></td>
</tr>
<tr>
<td>• Need for prolonged hospitalization</td>
<td></td>
</tr>
<tr>
<td>• Need for supplemental oxygen or intubation and ventilation</td>
<td></td>
</tr>
<tr>
<td>• History of apnea and bradycardia</td>
<td></td>
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<tr>
<td>• History of cardiovascular compromise</td>
<td></td>
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<tr>
<td>Other major illnesses and hospitalizations</td>
<td></td>
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<tr>
<td>Family history of anesthetic complications, malignant hyperthermia, or pseudocholinesterase deficiency</td>
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<tr>
<td>Respiratory problems:</td>
<td></td>
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<tr>
<td>• Long-term exposure to environmental tobacco smoke</td>
<td></td>
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<tr>
<td>• Obstructive apnea, breathing irregularities, or cyanosis (especially in infants younger than 6 mo of age)</td>
<td></td>
</tr>
<tr>
<td>• History of snoring or an obstructive breathing pattern</td>
<td></td>
</tr>
<tr>
<td>• Recent upper respiratory tract infection</td>
<td></td>
</tr>
<tr>
<td>• Recurrent respiratory infections</td>
<td></td>
</tr>
<tr>
<td>• Previous laryngotracheitis (croup) or laryngomalacia</td>
<td></td>
</tr>
<tr>
<td>• Asthma or wheezing during respiratory infections</td>
<td></td>
</tr>
<tr>
<td>• Airway abnormalities, facial anomalies, mucopolysaccharidosis</td>
<td></td>
</tr>
<tr>
<td>Cardiac problems:</td>
<td></td>
</tr>
<tr>
<td>• Murmur or history of congenital heart disease—ask for details</td>
<td></td>
</tr>
<tr>
<td>• Dysrhythmia</td>
<td></td>
</tr>
<tr>
<td>• Exercise intolerance</td>
<td></td>
</tr>
<tr>
<td>• Syncope</td>
<td></td>
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<tr>
<td>• Cyanosis</td>
<td></td>
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<tr>
<td>Gastrointestinal problems:</td>
<td></td>
</tr>
<tr>
<td>• Reflux and vomiting</td>
<td></td>
</tr>
<tr>
<td>• Feeding difficulties</td>
<td></td>
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<tr>
<td>• Failure to thrive</td>
<td></td>
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<tr>
<td>• Liver disease</td>
<td></td>
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<tr>
<td>Exposure to exanthems or potentially infectious pathogens</td>
<td></td>
</tr>
<tr>
<td>Neurologic problems:</td>
<td></td>
</tr>
<tr>
<td>• Seizures</td>
<td></td>
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<tr>
<td>• Developmental delay</td>
<td></td>
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<tr>
<td>• Neuromuscular diseases</td>
<td></td>
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<tr>
<td>• Increased intracranial pressure</td>
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<tr>
<td>Hematologic problems:</td>
<td></td>
</tr>
<tr>
<td>• Anemia</td>
<td></td>
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<tr>
<td>• Bleeding diathesis</td>
<td></td>
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<tr>
<td>• Tumor</td>
<td></td>
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<tr>
<td>• Immunocompromise</td>
<td></td>
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<tr>
<td>• Prior blood transfusions and reactions</td>
<td></td>
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<tr>
<td>Renal problems:</td>
<td></td>
</tr>
<tr>
<td>• Renal insufficiency, oliguria, anuria</td>
<td></td>
</tr>
<tr>
<td>• Fluid and electrolyte abnormalities</td>
<td></td>
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<tr>
<td>Psychosocial considerations:</td>
<td></td>
</tr>
<tr>
<td>• Posttraumatic stress</td>
<td></td>
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<tr>
<td>• Drug abuse, use of cigarettes or alcohol</td>
<td></td>
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<tr>
<td>• Physical or sexual abuse</td>
<td></td>
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<tr>
<td>• Family dysfunction</td>
<td></td>
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<tr>
<td>• Previous traumatic medical or surgical experience</td>
<td></td>
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<tr>
<td>• Psychosis, anxiety, depression</td>
<td></td>
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<tr>
<td>Gynecologic considerations:</td>
<td></td>
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<tr>
<td>• Sexual history (sexually transmitted infections)</td>
<td></td>
</tr>
<tr>
<td>• Possibility of pregnancy</td>
<td></td>
</tr>
<tr>
<td>Current medications:</td>
<td></td>
</tr>
<tr>
<td>• Prior administration of corticosteroids</td>
<td></td>
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<tr>
<td>Allergies:</td>
<td></td>
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<tr>
<td>• Drugs</td>
<td></td>
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<tr>
<td>• Iodine</td>
<td></td>
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<tr>
<td>• Latex products</td>
<td></td>
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<tr>
<td>• Surgical tape</td>
<td></td>
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<tr>
<td>• Food (especially soya and egg albumin)</td>
<td></td>
</tr>
<tr>
<td>Dental condition (loose or cracked teeth)</td>
<td></td>
</tr>
<tr>
<td>When and what the child last ate (especially in emergency procedures)</td>
<td></td>
</tr>
</tbody>
</table>
### Table 61-3: Specific Pediatric Diseases and Their Anesthetic Implications

<table>
<thead>
<tr>
<th><strong>DISEASE</strong></th>
<th><strong>IMPLICATIONS</strong></th>
<th><strong>DISEASE</strong></th>
<th><strong>IMPLICATIONS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RESPIRATORY SYSTEM</strong></td>
<td></td>
<td><strong>GASTROINTESTINAL</strong></td>
<td>Potential for reflux and aspiration</td>
</tr>
<tr>
<td>Asthma</td>
<td>Intraoperative bronchospasm that may be severe and even fatal</td>
<td></td>
<td>Potential for high overall morbidity and mortality in patients with hepatic dysfunction</td>
</tr>
<tr>
<td></td>
<td>Preoperative control is essential</td>
<td></td>
<td>Altered metabolism of many anesthetic drugs</td>
</tr>
<tr>
<td></td>
<td>Pneumothorax or atelectasis</td>
<td></td>
<td>Potential for coagulopathy and uncontrollable intraoperative bleeding</td>
</tr>
<tr>
<td></td>
<td>Optimal preoperative medical management is essential; preoperative steroids may be required</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Special equipment and personnel may be required</td>
<td></td>
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<tr>
<td></td>
<td>Should be anticipated in children with dysmorphic features or acute airway obstruction, as in epiglottitis or laryngotracheobronchitis or with an airway foreign body</td>
<td></td>
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<tr>
<td></td>
<td>Patients with Down syndrome may require evaluation of the atlantooccipital joint</td>
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<td></td>
<td>Patients with storage diseases may be at high risk</td>
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<tr>
<td></td>
<td>Barotrauma with positive pressure ventilation</td>
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<td></td>
<td>Oxygen toxicity, pneumothorax a risk</td>
<td></td>
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<tr>
<td></td>
<td>Airway reactivity, bronchornnea, increased intraoperative pulmonary shunt and hypoxia</td>
<td></td>
<td></td>
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<tr>
<td>Difficult airway</td>
<td>Risk of pneumothorax, pulmonary hemorrhage</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Atelectasis, risk of prolonged postoperative ventilation</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Patient should be assessed for cor pulmonale</td>
<td></td>
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<tr>
<td></td>
<td>Pulmonary hypertension and cor pulmonale must be excluded</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Careful postoperative observation for obstruction required</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BRONCHOPULMONARY DYSPLASIA</strong></td>
<td></td>
<td><strong>NEUROLOGIC</strong></td>
<td>Seizure disorder</td>
</tr>
<tr>
<td></td>
<td>Cystic fibrosis</td>
<td></td>
<td>Avoidance of anesthetics that may lower the seizure threshold</td>
</tr>
<tr>
<td></td>
<td>Sleep apnea</td>
<td></td>
<td>Optimal control ascertained preoperatively</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Preoperative serum anticonvulsant measurements</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Increased intracranial pressure</td>
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<td></td>
<td></td>
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<td>Neuror muscular disease</td>
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<td></td>
<td></td>
<td></td>
<td>Developmental delay</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Psychiatric</td>
</tr>
<tr>
<td><strong>CARDIAC</strong></td>
<td></td>
<td><strong>ENDOCRINE</strong></td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td>Need for antibiotic prophylaxis for bacterial endocarditis</td>
<td></td>
<td>Greatest risk is unrecognized intraoperative hypoglycemia; if insulin is administered, intraoperative blood glucose level monitoring needed; glucose and insulin must be provided, with adjustment for fasting condition and surgical stress</td>
</tr>
<tr>
<td></td>
<td>Use of air filters; careful purging of air from the intravenous equipment</td>
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<td></td>
<td>Physician must understand the effects of various anesthetics on the hemodynamics of specific lesions</td>
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<td></td>
<td>Preload optimization and avoidance of hyperviscous states in cyanotic patients</td>
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<tr>
<td></td>
<td>Possible need for preoperative evaluation of myocardial function and pulmonary vascular resistance</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Provide information about pacemaker function and ventricular device function</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HEMATOLOGIC</strong></td>
<td></td>
<td><strong>IMMUNOLOGIC</strong></td>
<td>Retroviral drugs may inhibit benzodiazepine clearance</td>
</tr>
<tr>
<td></td>
<td>Sickle cell disease</td>
<td></td>
<td>Immunodeficiency requires careful infection control practices</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Cytomegalovirus-negative blood products, irradiation, or leukofiltration may be required</td>
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<tr>
<td></td>
<td>Oncology</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Possible need for simple or exchange transfusion based on preoperative hemoglobin concentration and percentage of hemoglobin S</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Importance of avoiding acidosis, hypoxemia, hyperthermia, dehydration, and hyperviscosity states</td>
<td></td>
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<tr>
<td></td>
<td>Pulmonary evaluation of patients who have received bleomycin, bis-chloroethyl-nitrosourea, chloroethyl-cyclohexyl-nitrosourea, methotrexate, or radiation to the chest</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Avoidance of high oxygen concentration</td>
<td></td>
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<tr>
<td></td>
<td>Cardiac evaluation of patients who have received anthracyclines; risk of severe myocardial depression with volatile agents</td>
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<tr>
<td></td>
<td>Potential for coagulopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RHEUMATOLOGIC</strong></td>
<td></td>
<td><strong>METABOLIC</strong></td>
<td>Careful assessment of glucose homeostasis in infants</td>
</tr>
<tr>
<td></td>
<td>Limited mobility of the temporomandibular joint, cervical spine, artenoid cartilages</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Careful preoperative evaluation required</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Possible difficult airway</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Definitions of Anesthesia Care

### MONITORED ANESTHESIA CARE
A specific anesthesia service in which an anesthesiologist has been requested to participate in the care of a patient undergoing a diagnostic or therapeutic procedure.

Monitored anesthesia care includes all aspects of anesthesia care: a preprocedure assessment, intraprocedure care, and postprocedure anesthesia management.

During monitored anesthesia care, the anesthesiologist or a member of the anesthesia care team provides a number of specific services, which may include some or all of, but are not limited to, the following:

- Discussing anesthesia care with the family and child, obtaining consent, allaying anxiety and answering questions—family centered anesthesia care.
- Monitoring of vital signs, maintenance of the patient’s airway, and continual evaluation of vital functions.
- Diagnosing and treating clinical problems that occur during the procedure.
- Administering sedatives, analgesics, hypnotics, anesthetic agents, or other medications as necessary to ensure patient safety and comfort.
- Providing other medical services as needed to accomplish the safe completion of the procedure.

Anesthesia care often includes the administration of medications for which the loss of normal protective reflexes or loss of consciousness is likely.

**Monitored anesthesia care** refers to those clinical situations in which the patient remains able to protect the airway for the majority of the procedure.

If the patient is rendered unconscious and/or loses normal protective reflexes for an extended period, this is considered a general anesthetic.

### LIGHT SEDATION
Administration of anxiolysis and/or analgesia that obtunds consciousness but does not obtund normal protective reflexes (cough, gag, swallow, hemodynamic reflexes), or spontaneous ventilation.

### DEEP SEDATION
Sedation that obtunds consciousness and normal protective reflexes or possesses a significant risk of blunting normal protective reflexes (cough, gag, swallow, hemodynamic reflexes), hemodynamic and respiratory insufficiency may occur.

### GENERAL ANESTHESIA
Administration of hypnosis, sedation, and analgesia that results in the loss of normal protective reflexes.

### REGIONAL ANESTHESIA
Induction of neural blockade (either central, neuraxial, epidural, or spinal; or peripheral nerve block, e.g., digital nerve block, brachial plexus block), which provides analgesia and is associated with regional motor blockade.

Consciousness is not obtunded.

Special expertise is required.

Frequently, in children, anxiolysis and sedation are also necessary for this technique to be successful.

Regional anesthesia (e.g., caudal epidural blockade) is used to supplement general anesthesia and provide postoperative analgesia.

### LOCAL ANESTHESIA
Provision of analgesia by local infiltration of an appropriate anesthetic agent.

Does not require the presence or involvement of an anesthesiologist, although an anesthesiologist may provide local anesthesia services.

### NO ANESTHESIOLOGIST
An anesthesiologist will not be involved in the care of the child in any way.

---

**Table 61-4 Definitions of Anesthesia Care**

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
</table>
| MONITORED       | Provides other medical services as needed to accomplish the safe completion of the procedure.
| ANESTHESIA      | Administering sedatives, analgesics, hypnotics, anesthetic agents, or other medications as necessary to ensure patient safety and comfort. |
| CARE            | Diagnosing and treating clinical problems that occur during the procedure.                    |
| LIGHT           | Sedation that obtunds consciousness but does not obtund normal protective reflexes.          |
| SEDATION        | Administration of anxiolysis and/or analgesia that obtunds consciousness but does not obtund normal protective reflexes. |
| DEEP            | Sedation that obtunds consciousness and normal protective reflexes or possesses a significant risk of blunting normal protective reflexes. |
| GENERAL         | Administration of hypnosis, sedation, and analgesia that results in the loss of normal protective reflexes. |
| ANESTHESIA      | Induction of neural blockade (either central, neuraxial, epidural, or spinal; or peripheral nerve block, e.g., digital nerve block, brachial plexus block), which provides analgesia and is associated with regional motor blockade. |
| CARE            | Consciousness is not obtunded. Special expertise is required. Frequently, in children, anxiolysis and sedation are also necessary for this technique to be successful. Regional anesthesia (e.g., caudal epidural blockade) is used to supplement general anesthesia and provide postoperative analgesia. |
| LOCAL           | Provision of analgesia by local infiltration of an appropriate anesthetic agent.               |
| ANESTHESIA      | Does not require the presence or involvement of an anesthesiologist, although an anesthesiologist may provide local anesthesia services. |
| CARE            | An anesthesiologist will not be involved in the care of the child in any way.                  |

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Just as deleterious, physically and psychologically, as the painful procedures themselves. Management is aimed at blunting the fear and emotional response during surgery, painful procedures (bone marrow aspiration, lumbar punctures), or nonpainful but anxiety-provoking procedures (MRI, CT). Many drugs provide anxiolysis, blunting of recall, and amnesia for such events (Table 61-5). Obtundation of consciousness may accompany the provision of analgesia. Hypnotic and sedative agents can induce altered consciousness without producing any analgesia; analgesia and obtunded consciousness are not synonymous. It is also possible to provide analgesia (local, spinal, or epidural analgesia) without obtunding consciousness.

**Sedation** describes a medically induced state that is on a continuum between the fully alert, awake state and general anesthesia (see Table 61-4). In addition to inducing unconsciousness and amnesia, general anesthesia obtunds or ablates critical physiologic reflexes; the most important are airway-protective reflexes: coughing, gagging, and swallowing. Cardiorespiratory reflexes are also obtunded with general anesthesia; respiratory depression and hemodynamic compromise may occur and may be profound. As sedation deepens toward general anesthesia, loss of airway patency, loss of airway-protective reflexes, and loss of cardiovascular stability occur. Light (minimal) sedation is anxiolysis without loss of these reflexes or airway patency. Deep sedation occurs when these reflexes are obtunded or lost (see Table 61-4). Adequate sedation in children may be accompanied by the actual or potential loss of vital reflexes. It is mandatory that those providing sedation for a child be able to detect the transition into deep sedation and general anesthesia and be prepared to manage the child’s airway and circulation, and provide CPR if required.

**Akinesia (Immobility or Muscular Relaxation)**

Akinesia is the absence of movement. It is necessary to ensure safe and adequate operative conditions and to provide ideal conditions for advanced and meticulous surgery. Akinesia is often produced with muscle relaxants (see Table 61-5). These agents facilitate respiratory management in the perioperative period and in critically ill patients. The absence of movement is neither the absence of pain nor the presence of amnesia. **Whenever neuromuscular blocking agents are used, analgesia and sedation must be provided.**

**Physiologic Support**

The need for anesthesia increases the need to monitor and support physiologic integrity and homeostasis. Sedation and anesthesia have significant and potentially life-threatening physiologic consequences (see Tables 61-4 and 61-5). Maintenance of adequate cardiopulmonary function, fluid management, electrolyte control, thermoregulation, and concern for all aspects of the child’s health are critical during anesthesia.

**Vigilance**

Constant, critical attention by physicians who understand the demands of the surgical procedure, as well as the changes in physiologic status and their implications, is mandatory to provide safe perioperative care.
<table>
<thead>
<tr>
<th>Table 61-5</th>
<th>Selected Drugs Used in Anesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DRUG</strong></td>
<td><strong>USES AND IMPLICATIONS</strong></td>
</tr>
<tr>
<td><strong>MUSCLE RELAXANTS</strong></td>
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</tr>
</tbody>
</table>
| Succinylcholine | Used to facilitate endotracheal intubation and maintain muscle relaxation in emergency situations; now virtually never given routinely  
| | A depolarizing neuromuscular blocking agent with rapid onset and offset properties  
| | Associated with the development of malignant hyperthermia in susceptible patients  
| | Degraded by plasma cholinesterase, which may be deficient in some individuals; such a deficiency may result in prolonged effect  
| | Fasciculations may be associated with immediate increases in intracranial and intraocular pressures as well as postoperative muscle pain  
| | Nondepolarizing neuromuscular blockers  
| | Vecuronium, rocuronium, mivacurium, cis-atracurium, all aminosteroids  
| | Have less-rapid onset than succinylcholine but are longer-acting  
| | Prolonged ICU use may lead to profound muscle weakness  
| | Vecuronium and rocuronium are metabolized by the liver and excreted in bile; they are the most commonly used neuromuscular blocking agents  
| | cis-Atracurium is metabolized by plasma cholinesterase and therefore may be of benefit in patients with hepatic or renal disease |
| **HYPNOTICS** |                       |
| Propofol | Rapidly acting hypnotic; amnestic, but not analgesic, a general anesthetic agent  
| | Like pentothal, may cause hypotension  
| | Causes respiratory depression  
| | May increase the seizure threshold  
| | Great utility in titrated doses for sedation and with local anesthetic and short-acting opioid for outpatient procedures  
| | May suppress nausea  
| | Associated with the often fatal propofol infusion syndrome when used in prolonged intravenous infusion (>24 hr) and therefore not used for ICU sedation in children  
| Etomidate | Cardiovascular stability on induction with no increase in intracranial pressure  
| | Inhibits corticosteroid synthesis and increases ICU mortality  
| | Associated with myoclonus, potential difficulty with assisted ventilation, and pain on injection  
| Ketamine | Hypnotic analgesic and amnestic  
| | Causes sialorrhea and should be coadministered with an antisialagogue, such as atropine or glycopyrrolate  
| | May be associated with laryngospasm  
| | Causes endogenous catecholamine release, tachycardia, and bronchodilation  
| | Increases intracranial and intraocular pressures  
| | Decreases the seizure threshold  
| **SEDATIVE–ANXIOLYTICS** |                       |
| Benzodiazepines | Produce sedation, anxiolysis, or hypnosis, depending on the dose  
| | May produce antegrade, but not retrograde, amnesia  
| | All agents raise the seizure threshold, are metabolized by the liver, and depress respiration, especially when administered with opioids  
| | Frequently administered as premedications  
| | Diazepam may be painful on injection and has active metabolites  
| | Midazolam can be administered by various routes and has a short half-life  
| | Lorazepam has no active metabolites  
| | Sedation effected by all benzodiazepines may be reversed by flumazenil, but respiratory depression may not be reliably reversed  
| Dexmedetomidine | Produces anxiolysis, sedation, sympatholysis, by $\alpha_2$-receptor stimulation centrally; has mild analgesic properties  
| | Side effects include hypotension and bradycardia  
| | Commonly used for procedural and ICU sedation  
| | Continuous infusion for ICU sedation; currently limited to 24 hr  
| **ANALGESIC–SEDATIVES** |                       |
| Opioids | Gold standard for providing analgesia  
| | All cause respiratory depression  
| | Morphine and, to a lesser extent, hydromorphone may cause histamine release  
| | The synthetic opioids fentanyl, sufentanil, and short-acting alfentanil may have a greater propensity to cause chest wall rigidity when administered rapidly or in high doses and are also associated with the rapid development of tolerance; these 3 drugs have particular utility in cardiac surgery because of the hemodynamic stability associated with their use  
| | Remifentanil is an ultra–short-acting synthetic opioid that is metabolized by plasma cholinesterase; it may have particular utility when deep sedation and analgesia are required along with the ability to assess neurologic status intermittently  
| **INHALATIONAL AGENTS** |                       |
| Nitrous oxide | Causes amnesia and mild analgesia at low concentrations  
| | Danger of hypoxic mixture if the oxygen concentration is not monitored and preventive safety mechanisms are not in place  
| | “Complete anesthetics”—they induce a state of hypnosis, analgesia, and amnesia  
| | All are myocardial depressants, and some are vasodilators  
| | May trigger malignant hyperthermia in susceptible individuals  
| Potent vapors, sevoflurane, desflurane, isoflurane | Sevoflurane is almost universally used for inhalation induction of anesthesia in children  
| | All are bronchodilators at equipotent concentrations  
| | Isoflurane, and especially desflurane are associated with a higher incidence of laryngospasm, when used for anesthetic induction, than sevoflurane  
| | Causes amnesia and mild analgesia at low concentrations  
| | Danger of hypoxic mixture if the oxygen concentration is not monitored and preventive safety mechanisms are not in place  
| | “Complete anesthetics”—they induce a state of hypnosis, analgesia, and amnesia  
| | All are myocardial depressants, and some are vasodilators  
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| | Sevoflurane is almost universally used for inhalation induction of anesthesia in children  
| | All are bronchodilators at equipotent concentrations  
| | Isoflurane, and especially desflurane are associated with a higher incidence of laryngospasm, when used for anesthetic induction, than sevoflurane |
for all children. Careful attention to a child’s preoperative condition is mandatory for minimizing the risk during perioperative care (see Tables 61-3 and 61-4).

**INDUCTION OF GENERAL ANESTHESIA**

The goal of induction of general anesthesia is to rapidly achieve surgical anesthesia by using IV or, more commonly in children, inhalational induction agents. In children who are too young to tolerate the establishment of vascular access before the induction of anesthesia, it is routine to induce anesthesia by mask inhalation of volatile anesthetics. In the operating room, a child is often accompanied by the parents (parental presence during induction [PPPI]) and placed on the operating room table. Before the induction of anesthesia, monitors are usually applied to the child. These include a pulse oximeter, electrocardiogram, and a blood pressure cuff. The child is then cautiously introduced to the face mask, which contains a high gas flow (5-7 L/min of oxygen), frequently mixed with nitrous oxide. Inhalation of nitrous oxide and oxygen for 60-90 sec induces a state of euphoria. The airway responses to inhalational anesthetics are now blunted, and sevoflurane can be introduced into the inhaled gas mixture. This leads to unconsciousness within 30-60 sec while the child continues to breathe spontaneously.

The child is now “asleep,” and the parents can be asked to leave. An IV line is then started, and comprehensive intraoperative monitoring initiated. Surgical anesthesia can be maintained by spontaneous ventilation with a mask; this is safe only when the airway is secure and patent, the stomach is empty, and the child is older than 6 mo of age. Procedures longer than 1 hr are not usually performed with mask inhalational anesthesia. If these conditions are not met, if the surgeon needs to approach the airway, or if muscular paralysis is required, then the airway must be secured with endotracheal intubation. Although endotracheal intubation can be performed under deep inhalational anesthesia with respiratory depression and obtunded cough and gag reflexes, the depth of anesthesia required to ablate airway reflexes is very close to the level that induces hemodynamic instability. Therefore, muscle relaxation with IV, nondepolarizing muscle relaxants is induced to facilitate endotracheal intubation. Succinylcholine is rarely, if ever, used. After paralysis is induced, direct laryngoscopy and airway intubation can be performed. Correct endotracheal tube placement is confirmed by direct laryngoscopy, end-tidal CO₂ measurement, endotracheal tube fogging, and the finding of bilaterally equal breath sounds during positive-pressure ventilation. If necessary, fiberoptic airway endoscopy and chest radiograph, in addition to these measures, can be used to confirm correct endotracheal tube placement.

After endotracheal intubation, spontaneous ventilation may be permitted, if muscle relaxants are not used or have worn off; it is routine to provide controlled mechanical ventilation. When the child is completely anesthetized, positioned for surgery, and hemodynamically stable, and maintenance anesthesia is achieved, the surgery can begin.

**Inhalational Anesthetics**

General anesthesia may be induced and maintained by either inhalation or the IV route. The inhalational anesthetics used in children include sevoflurane, isoflurane, and desflurane. Although halothane is the prototypical pediatric inhalational anesthetic agent, it has been replaced by sevoflurane and is no longer used in the United States. The minimal alveolar concentration (MAC) of an inhalational anesthetic is the alveolar concentration (expressed as percent at 1 atmosphere) that provides sufficient depth of anesthesia for surgery in 50% of patients. For potent inhalational agents, the alveolar concentration of an anesthetic reflects the arterial concentration of anesthetic in the blood perfusing the brain. Thus, the MAC is an indication of anesthetic potency and is analogous to the ED₉₀ (effective dose in 50% of recipients) of a drug. MAC is age-dependent, is lower in premature infants than in full-term infants, and decreases from term through infancy to preadolescence. In adolescence, MAC again increases, falling thereafter. Inhalational anesthetic agents are poorly soluble in blood but rapidly equilibrate between alveolar gas and blood.

**Respiratory Effects**

The advantages of inhalational anesthesia are rapid onset, rapid offset, convenient route of delivery and excretion (respiratory), and the ability to provide profound analgesia and amnesia. Inhalational anesthetics are all airway irritants and, in low doses, can cause laryngospasm. All inhalational anesthetics depress ventilation in a dose-dependent manner. Thus, expired CO₂ and PaCO₂ (arterial partial pressure of carbon dioxide) increase in spontaneously breathing children. In addition, anesthesia also decreases end-expiratory lung volume. Small lung volumes result in a decrease in lung compliance, increases in total pulmonary resistance, work of breathing, and intrapulmonary arteriovenous shunting, and a restrictive lung defect. Inhalational anesthetics also shift the CO₂ response curve to the right, thus decreasing, but not abating, the increase in minute ventilation with increasing PaCO₂.

Inhalational anesthetics, which may induce apnea and hypoxia in premature infants and newborns, are less frequently used in premature infants and children. In neonates and young infants, general anesthesia always necessitates endotracheal intubation and controlled mechanical ventilation. In older children, spontaneous breathing through a mask or a laryngeal mask airway without controlled ventilation is possible for shorter operations. The decreased end-expiratory lung volume and increased work of breathing always necessitate higher inspired oxygen tension.

**Cardiovascular Effects**

Cardiovascular effects of inhalational anesthesia include depressed cardiac output and peripheral vasodilation; hypotension is frequent. This is accentuated in hypovolemic patients. This hypotensive effect is more pronounced in neonates than in older children and adults. Inhalational anesthetics also decrease baroreceptor and heart rate responses. Inhalational anesthesia blunts the hypoxic pulmonary vasmotor response in the pulmonary circulation, an effect that may contribute to hypoxemia.

The net effect of inhalational anesthesia is decreased oxygen delivery. Perioperatively, catabolism is enhanced and oxygen demand is increased; there may be a profound imbalance between oxygen demand and oxygen delivery. Development of a metabolic acidosis intraoperatively may reflect this imbalance. Because the cardiovascular depressant effects of inhalational anesthesia are greater in premature and newborn infants, these agents are of limited use in such patients.

All inhalational anesthetic agents cause cerebrovasodilation. Sevoflurane is a more potent cerebrovasodilator than isoflurane. Thus, in children with elevated intracranial pressure, impaired cerebral perfusion, or head trauma, and in premature neonates at risk for intraventricular hemorrhage, inhalational anesthetics should be used with extreme caution. Although inhalational anesthetics decrease cerebral oxygen consumption, they may disproportionately decrease blood flow; thus worsening oxygen delivery.

**Specific Anesthetics**

**Sevoflurane**

Sevoflurane is the most commonly used inhalational anesthetic in children for both induction and maintenance of general anesthesia. It is not a significant airway irritant and leads to smoother induction than isoflurane. Emergence from sevoflurane anesthesia is quite rapid; there is a significant amount of emergence delirium, especially if pain has been inadequately controlled or induction was stormy and preoperatively anxiety high. This effect can be blunted by pretreatment with midazolam and adequate use of opioids, although the latter delay recovery from anesthesia. Metabolism of sevoflurane yields free fluoride, which may cause renal damage; consequently, the FDA has restricted the use of sevoflurane to <2 MAC hr, preferably with fresh gas flow rates >2 L/min.

**Isoflurane**

Isoflurane maintains cardiac output and cerebral perfusion more effectively than sevoflurane. Isoflurane is pungent and a significant airway irritant, with an unacceptably high incidence of complications, such as laryngospasm during induction. Emergence from anesthesia with
isoflurane is quite smooth, but slower than for sevoflurane. Cerebral blood flow is only minimally affected, and cerebral oxygen delivery is maintained. Because isoflurane is not a suitable induction agent, induction with sevoflurane or with an intravenous agent, and maintenance with isoflurane is a common pediatric anesthesia practice.

Desflurane
A potent airway irritant, desflurane causes coughing, breath holding, and laryngospasm during induction and therefore is unsuitable for induction. It is frequently used for maintenance of anesthesia, and emergence from desflurane anesthesia is rapid.

Nitrous Oxide
Nitrous oxide is a tasteless, colorless, odorless gas with potent analgesic properties. It induces a state of euphoria (hence its nickname, “laughing gas”). The MAC of nitrous oxide is >100; consequently, it is not suitable as a sole agent to maintain anesthesia. Nevertheless, nitrous oxide has few complications and produces little or no hemodynamic or respiratory depression. Commonly, during maintenance of general anesthesia, the inhalational gas mixture is 70% nitrous oxide and 30% oxygen, with the addition of an inhalational anesthetic or potentiation of analgesia with an opioid or a hypnotic agent. The deleterious effects of nitrous oxide are increased postoperative nausea and vomiting and, with long-term use (days), bone marrow suppression. Although there is no evidence of harmful sequelae of the use of nitrous oxide for routine anesthesia, its use has decreased because of the greater incidence of nausea and vomiting associated with it. Nitrous oxide is a potent anesthetic that is safely used in a mixture of 50% nitrous oxide and oxygen (Entonox) in obstetrics and in emergency departments to provide analgesia. Although this combination appears to be safe, it potentiates the respiratory depressive effects of opioids, and its use, in combination with any other sedative, hypnotic, or opioid agent, requires very close monitoring because it may produce general anesthesia.

Intravenous Anesthetic Agents
Anesthesia can be both induced and maintained with either intermittent boluses or continuous infusions of IV anesthetic agents. Intravenous anesthetics include barbiturates, opioids, benzodiazepines, and miscellaneous drugs, such as propofol and ketamine. Intravenous anesthetic agents can induce anesthesia more rapidly than inhalational anesthetics, with fewer complications. Vascular access is required, so unless IV access has already been obtained, inhalation induction is the preferred route. For children arriving in the operating room with vascular access, IV induction should be routine, because it rapidly takes the child from the awake state to the anesthetized state with less psychologic and cardiorespiratory compromise than occurs with inhalational induction. All IV agents affect cardiorespiratory function. The 1 exception to this may be ketamine, which, in lower doses, releases catecholamines, which maintain cardiac function and blood pressure.

Propofol
Propofol is the most commonly used IV induction agent in pediatric anesthesiology and has a rapid onset. In doses of 2-3 mg/kg, propofol induces both respiratory depression and hypotension. Propofol can sometimes burn and itch on injection. It is formulated in 10% soy emulsion with egg emulsifiers, so is contraindicated in patients with soy or egg allergy. After induction of anesthesia, propofol is also a useful agent for maintaining hypnosis and amnesia, and can be used as a sole anesthetic agent for nonpainful procedures, such as radiation therapy, MRI, and CT studies. Combined with opioids, it provides excellent, brief anesthesia for painful procedures, such as lumbar puncture and bone marrow aspiration. Propofol is a general anesthetic agent that obviates airway reflexes, respiration, and hemodynamic function; it should not be considered a “sedation agent.” Although hemodynamic stability, and even spontaneous respirations, can be maintained with cautious propofol sedation, its use for prolonged sedation over several hours to days in children younger than 12 yr is associated with hemodynamic collapse, bradycardia, metabolic acidosis, cardiac failure, rhabdomyolysis, hyperlipidemia, profound shock, and death (propofol infusion syndrome). Its use for prolonged sedation (>12 hr) in the critical care setting in children is contraindicated.

Barbiturates
The most commonly used barbiturate for IV induction is sodium thiopental, although it is now rarely used. Although loss of consciousness is rapid, barbiturates do not provide analgesia. Thiopental depresses respiration, induces apnea, and can cause hypotension in the hypovolemic patient. Induction with 3-5 mg/kg of thiopental usually produces 5-10 min of unconsciousness within seconds. After IV induction with sodium thiopental, maintenance anesthesia can be established using benzodiazepines, IV opioids, or inhalational anesthetics.

Pentobarbital is commonly used for sedation in children. It is an IV drug that induces loss of consciousness. It is also a potent respiratory depressant, particularly when used in conjunction with opioids and benzodiazepines. Pentobarbital has a very prolonged effect. It is not an analgesic agent, and painful procedures cannot be performed with pentobarbital sedation without supplemental analgesia. Pentobarbital sedation that is deep enough for anxioysis and nonpainful procedures generally results in prolonged sleep. Its potency and long duration of action make it difficult to titrate. It is not an ideal drug for sedation for short or painful procedures.

Sodium methohexital (Brevital) is another IV induction agent. It is similar to sodium thiopental and has a similar spectrum of respiratory depression.

Etomidate
Etomidate is an imidazole derivative used for the induction of anesthesia, frequently in emergency situations. Its action is not as rapid as that of propofol. The lack of cardiovascular depression has led to the use of etomidate in patients with hemodynamic compromise, cardiac disease, and septic shock. Unfortunately, by inhibition of 11β-hydroxylase, this agent depresses synthesis of both mineralocorticoids and glucocorticoids for up to 72 hr following a single induction dose. Etomidate increases mortality when used as a sedative in ICUs (for which it is now contraindicated) and when used in patients who receive merely an induction dose. Adrenal suppression by etomidate further complicates the management of the very patients with hemodynamic compromise in whom the agent has been indicated. The decision to continue use of this agent must weigh the serious risks against the short-term benefit of hemodynamic stability during anesthesia induction and sedation.

Ketamine
Ketamine rapidly induces general anesthesia that lasts for 15-30 min when given at 1-3 mg/kg IV. It has few side effects and can maintain adequate blood pressure and cardiac output. Ketamine is also effective when given intramuscularly, subcutaneously, nasally, or orally; the dose must be increased for these alternative routes. Ketamine dissociates the connections between the cortex and limbic system (dissociative anesthesia) by its inhibition of N-methyl-D-aspartate receptors, producing a unique anesthetic state. Ketamine is not only a hypnotic agent, providing obtundation and loss of consciousness, but also an analgesic agent, and can act as a sole IV agent to provide general anesthesia. With low doses of this agent, airway reflexes and spontaneous ventilation may be maintained; at higher doses, loss of airway reflexes, apnea, and respiratory depression occur. It is unwise to rely on ketamine to prevent aspiration of gastric contents during deep sedation. Intravenous ketamine is a useful general anesthetic agent for short procedures.

Ketamine produces disturbing postanesthetic dreams and hallucinations. These can occur at the time of emergence from anesthesia and for several weeks. In adults, the incidence of this effect is 30-50%; in prepubertal children, it may be 5-10%. Premedication with a benzodiazepine, such as midazolam, greatly reduces these sequelae; a benzodiazepine is routinely given to children receiving ketamine anesthesia. The other side effect of ketamine is that it is a potent secretagogue, enhancing oral and bronchial secretions. A drying agent, such as atropine or glycopyrrolate, is administered before the administration of ketamine.
A bronchial smooth muscle relaxant (bronchodilator), ketamine is a useful agent for sedating asthmatic patients and others in the ICU. Ketamine has been reported to increase intracranial pressure and therefore is not indicated in patients at risk for elevated intracranial pressure. Ketamine can increase myocardial oxygen demand and should be used cautiously in patients with impaired myocardial oxygen delivery or cardiac outflow tract obstruction.

**Opioids**

Opioids are superb analgesic agents, providing analgesia for painful procedures and postprocedural pain (see Chapter 62). Large doses of morphine (0.5-2 mg/kg), combined with nitrous oxide, provide adequate analgesia for painful procedures and surgery. Opioids suppress the CO2 response, can induce apnea, and are respiratory depressants. Morphine is often associated with hypotension and bronchospasm from histamine release; it is used with caution in children with asthma. Morphine is a long-acting agent, and an equivalent dose per kilogram gives much higher blood levels in neonates than in older children, with plasma concentrations approximating 3 times those in adults. This reason for this difference is the longer elimination half-life (14 hr) in children than in adults (2 hr). Because of the prolonged activity and hemodynamic instability induced by morphine, the fentanyl class of synthetic opioids has replaced it.

**Fentanyl** is an effective agent to provide pain relief, analgesia, and sedation for painful procedures, with a shorter duration of action and a more stable hemodynamic profile than morphine. In equal analgesic doses, all opioids are equally potent respiratory depressants. Other anesthetic agents potentiate this respiratory depression, whether they are inhalational anesthetics or IV barbiturates or benzodiazepines.

Fentanyl use at 30-50 µg/kg obtunds the hemodynamic response to surgery and provides stable operating conditions. Effective analgesia and anesthesia can be provided with IV fentanyl in a 2-3 µg/kg bolus followed by a 1-3 µg/kg/hr continuous infusion. Hemodynamic effects can be blunted and recall totally obtunded with use of a nitrous-narcotic anesthetic technique, although muscle tone may remain high and spontaneous movements can occur. Nitrous-narcotic anesthetics usually are supplemented with a nondepolarizing muscle relaxant during maintenance anesthesia. If the patient will be extubated and resume spontaneous ventilation, reversal of the muscle relaxant is necessary.

Other synthetic opioids (sufentanil, alfentanil, remifentanil) are available, but fentanyl is the most commonly used opioid. Both sufentanil and alfentanil have been used for cardiac anesthesia; their potency is different from that of fentanyl. Alfentanil appears to cause an increased incidence of muscle rigidity, convulsions, and prolonged respiratory depression compared with fentanyl, and is not used in children.

**Remifentanil** has very rapid onset and offset of action. In doses of 0.25 µg/kg/min, surgical anesthesia can be maintained with this agent. Its short half-life and rapid offset are advantageous for rapid emergence from anesthesia. Unfortunately, its rapid offset of action also leads to postprocedural and postoperative pain and requires analgesic supplementation, frequently with an opioid, which removes the advantage of anesthesia with a short-acting opioid. Remifentanil may have a role in providing rapidly deepening anesthesia for particularly painful events or rapidly inducing analgesia. It is also used intraoperatively by continuous infusion to maintain anesthesia. It is a potent respiratory depressant and provides no postprocedural analgesia, features that limit its use.

**Benzodiazepines**

Benzodiazepines induce hypnosis, anxiolysis, sedation, and amnesia, and have anticonvulsant activity. In larger doses, they cause respiratory depression and apnea; they are synergistic with opioids and barbiturates in their respiratory depressant effects. Benzodiazepines are γ-aminobutyric acid agonists.

The most commonly used benzodiazepine in pediatric anesthesia is midazolam. Short acting and water soluble, it can be injected intravenously without pain. It is a potent hypnotic—anxiolytic—anticonvulsant and is approximately 4 times more potent than diazepam. In anxiolytic doses, midazolam (0.15 mg/kg) has no effect on respiratory rate, heart rate, or blood pressure, and provides excellent preoperative sedation that is frequently accompanied by amnesia. It can be administered orally, nasally, rectally, intravenously, or intramuscularly. Use of oral midazolam at a dose of 0.5-1.0 mg/kg, mixed in sweet, flavored syrup, induces anxiolysis in approximately 90% of children. This agent has no hemodynamic, oxygenation, or respiratory depressant effects at this dose level, but when midazolam is used as a sole agent, children may frequently lose their balance and head control, may have blurred vision, and, rarely, may become dysphoric. A child sedated with midazolam should not be left unattended and is not safe walking. Most children rapidly accept an inhalational anesthetic mask after oral midazolam premedication. The widespread use of preoperative oral midazolam has decreased the practice of PPI to calm younger children.

**Dexmedetomidine**

Dexmedetomidine is an IV agent that obtunds consciousness through central α2-receptor stimulation, much like clonidine. It appears to cause no respiratory depression and produces anxiolysis, sedation, and mild analgesia. It is a sympatholytic, and its side effects include hypotension and bradycardia. Dexmedetomidine is commonly used for sedation in ICU patients as well as for procedures; it is being explored as an adjuvant for general anesthesia, especially in cardiac patients.

**Complications During Induction of Anesthesia**

The period between full wakfulness, with the child in control of airway reflexes, and general anesthesia, with total loss of control, is fraught with difficulty. During induction, laryngospasm, bronchospasm, vomiting, pulmonary aspiration of gastric contents, and subsequent aspiration pneumonitis pose a constant threat although they rarely occur. Concern about vomiting and aspiration dictates the use of preanesthetic fasting (NPO [nothing by mouth]) guidelines and indicates rapid sequence anesthetic induction.

**Laryngospasm** is the most common complication. During induction of anesthesia, especially with inhalational anesthetics, a period of excitement may occur. This period is associated with heightened airway reflexes, which can lead to coughing, gagging, laryngospasm, and bronchospasm. Laryngospasm is reflex closure of the larynx, which makes it impossible for the child to breathe or for assisted ventilation to be used. The child may make violent inspiratory efforts against a closed glottis, generating significantly negative intrathoracic pressure. This may affect cardiovascular function and cause postobstructive pulmonary edema. Laryngospasm can be prolonged, and hypoxia may ensue. Laryngospasm occurs in up to 2% of all anesthetic inductions in children younger than 9 yr and is half as common in older patients. Laryngospasm occurs twice as frequently in children with active or recent upper respiratory tract infection (URI). A history of passive smoking from environmental (parental) tobacco smoke increases the likelihood of laryngospasm 10-fold, and even more if the smoker is the child’s mother.

Laryngospasm can be relieved during induction of anesthesia by increasing the anesthetic dosage, either intravenously or through inhalation (although with the glottis closed, further administration of inhalational anesthesia is not possible). Muscle relaxation relieves laryngospasm, and in an acute situation, this situation may be an indication for succinylcholine. Constant positive airway pressure administered by someone skilled in airway management to ensure patency of the soft tissues of the oropharynx may be beneficial in alleviating laryngospasm. Laryngospasm may also occur during emergence from anesthesia, because a state of excitement is again traversed between deep anesthesia and wakfulness.

**Bronchospasm** can occur during induction, either in response to histamine release as a result of many of the anesthetic agents or as part of a hyperexcitable stage. Endotracheal intubation may also induce bronchospasm during induction. Bronchospasm during induction is particularly common in children with asthma. Bronchospasm secondary to intubation in a patient with reactive airway disease can be severe, may be associated with life-threatening hypoxemia, and may make it
impossible to ventilate the child. The use of histamine-releasing anesthetic agents has been associated with total airway obstruction, respiratory failure, and cardiac arrest. Environmental tobacco smoke is a risk factor.

Other pulmonary problems with induction of anesthesia include massive atelectasis with hypoxemia, impaired ventilation and perfusion, blunted hypoxic pulmonary vasoconstriction, and increased airway secretions with decreased bronchial function. Hypersecretion is prevented by the routine use of antialagouges, such as atropine. The newer inhalation agents are less-potent secretagouges, and the use of atropine premedication is much less common, but is probably indicated if ketamine is used.

Hemodynamic complications upon anesthesia induction include hypotension, which can be profound in hypovolemic patients; decreased myocardial function, which can be severe in patients with compromised cardiac function; and tachycardia and cardiac dysrhythmias. Inhalational anesthetics sensitize the myocardium to circulating catecholamines, and induction and excitement are associated with a hypercatecholaminergic state.

**Parental Presence During Induction of Anesthesia**

Parents may expect to be with their child during the induction of anesthesia. Removing a terrified child from the comforting arms of a parent is stressful for the child, the parent, and the caregivers. If this parental separation cannot be achieved comfortably with preoperative psychoprophylaxis and behavioral modification, including education and desensitization to the operative environment, or with pharmaco-logic aids, such as preoperative medications including benzodiazepine and barbiturates, then there may be a need to defer parent–child separation until general anesthesia is induced. Preoperative medication with oral benzodiazepine more frequently provides calm, smooth induction conditions than PPI without pharmacologic preparation. Although the use of PPI in the hands of a confident, competent anesthesia practitioner can replace the need for preoperative medication, it does not reliably predict smooth induction. PPI appears to decrease neither emergence phenomena nor the incidence of postoperative behavioral changes, and it does not appear to add an advantage for the child over that provided by preoperative sedative medication, such as with oral midazolam.

**Maintenance of Anesthesia**

Maintenance of anesthesia is the period between induction and emergence. The child should be asleep, unaware of pain, unresponsive with either motion or hemodynamic responses to painful stimuli, and homeostatically supported. The child is comatose, without airway-protective reflexes and with suppression or absence of respiration, and has received drugs that suppress hemodynamic adaptive responses. The child is also exposed to surgical trauma, and there may be blood loss and significant fluid shifts (third spacing), decreased intravascular volume, and hypothermia.

Anesthesia is usually maintained with or without nitrous oxide, an inhalational anesthetic such as isoflurane or sevoflurane, and an opioid for intraoperative analgesia, potentiation and deepening of anesthesia, and postoperative analgesia. A benzodiazepine is added either during premedication or intraoperatively to supplement hypnosis and amnesia. A nondepolarizing muscle relaxant (vecuronium or rocuronium) completes the pharmacologic maintenance of anesthesia. Agents can be given by continuous inhalational anesthesia or by continuous or bolus IV infusion.

During maintenance, the child may breathe spontaneously through an anesthetic mask or endotracheal tube or may be mechanically ventilated. All general anesthetic agents decrease end-expiratory lung volume, which is generally lower than functional residual capacity, with increases in pulmonary closing capacity and intrapulmonary shunt. Hypoxia would occur without supplemental oxygenation. These effects are compounded by respiratory depressant effects and the depressed CO₂ response curve. Therefore, it is generally considered that use of anesthetics for longer than 1 hr requires endotracheal intubation and positive-pressure ventilation. For long procedures, spontaneous breathing through a mask is possible; in smaller children, in whom the surgical field and the airway may be close together, the need to maintain a patent airway necessitates endotracheal intubation.

**Muscle relaxation** to facilitate endotracheal intubation was once accomplished with succinylcholine. This agent has a high-risk profile, however, and is associated with postoperative pain (muscle spasms); hyperkalemia; elevated intracranial, intraocular, and intragastric pressures; malignant hyperthermia; and myoglobinuria and renal damage. Succinylcholine is now rarely used, except to provide rapid relief of laryngospasm. Intubation of the airway is facilitated with a nondepolarizing, short-acting muscle relaxant. Rocuronium is the drug most commonly used for intubation. After intubation of the airway, the decision must be made whether to maintain muscle relaxation to facilitate surgery or to allow the child to resume spontaneous respiration. Prolonged use of a nondepolarizing muscle relaxant is common practice but may contribute to postoperative respiratory compromise if it is not fully reversed with appropriate agents.

**Reversal of neuromuscular blockade** is standard anesthetic practice. Effects of nondepolarizing muscle relaxants are reversed by increasing the concentration of acetylcholine with neostigmine (ace-tylcholine esterase inhibitor) and either atropine or glycopyrrolate to prevent the vagal effects. With the virtual abandonment of succinylcholine, only nondepolarizing muscle relaxants are routinely used for intubation. The termination of their action depends on metabolism and elution away from the neuromuscular junction. This process, even for the shortest-acting muscle relaxants (rocuronium), can take several minutes. An intubating dose of rocuronium to rapidly induce paralysis in emergency situations may not spontaneously reverse for 20 min or longer (compared with ~3 min for succinylcholine). If the airway cannot be secured, disaster may follow in the child who is unable to breathe spontaneously and in whom blockade cannot be reversed.

**Thermoregulation** is critical during anesthesia. The absence of movement and the inhibition of shivering lead to difficulty in thermogenesis. All the contributors to heat loss—convection, radiation, evaporation, and conduction—occur during anesthesia. Humidification and warming of inspired air are required. Additional warming devices are commonly used, such as rewarmin blankets. General anesthetic increase the interthreshold range (the minimal temperature change that will lead to sympathetic response, generally 0.3°C [0.5°F]). Although temperature sensing may remain normal, an autonomic response to hypothermia is not triggered. Anesthetic agents cause vasoparesis, which further impedes thermoregulation and increases heat loss. In newborns, inhalational anesthetics inhibit noshivering thermogenesis from brown fat, putting them at higher risk for hypothermia.

**Fluid Maintenance During Surgery and Anesthesia**

Patients who are unconscious and immobile have lost venous pump mechanisms and have peripheral venous pooling. Anesthetic agents cause vasodilation, and anesthetized patients have relative hypovolemia. Intravascular volume expansion is frequently required after the induction of anesthesia to maintain adequate perfusion, tissue oxygenation, urine output, and blood pressure. Volume expansion is most commonly provided by isotonic salt-containing solutions (normal saline, lactated Ringer solution). Autonomic responses may be increased as part of the surgical stress response, with vasoconstriction and intravascular volume contraction caused by diuresis, intravascular volume loss from hemorrhage, evaporation (insensible loss, increased during surgery), and third space (interstitial space) fluid losses resulting from the inflammatory response. Abnormalities in the distribution of renal blood flow and secretion of antidiuretic hormone further complicate the regulation of intravascular volume.

The concern about **hypoglycemia** as a result of preoperative fasting led to the recommendation that infants and small children receive
isotonic solutions with 5% glucose. The occurrence of hyperglycemia and potential neurologic injury during cardiopulmonary bypass, or during neurosurgery and other situations in which central nervous system injury can occur, however, along with the recognition that hypoglycemia is rare in nonneonates, has called into question the routine use of glucose-containing solutions. In neonates, glucose monitoring during and after anesthesia is indicated. In older children with normal nutritional status, isotonic salt solutions without additional glucose are adequate. In children who are receiving parenteral alimentation with a solution containing a high glucose concentration (>10%), continuation of the glucose concentration should be ensured to avoid rebound hypoglycemia, which would occur if the high-glucose solution was stopped.

Intraoperative fluid maintenance includes (1) current maintenance fluids and replacement of usual deficits during the NPO period; (2) replacement of third space losses; and (3) replacement of extraordinary losses (hemorrhage). Infants should receive glucose-containing isotonic fluids, such as 5% dextrose in water with either 0.25 normal saline or isotonic crystalloid solutions. Table 61-6 is a guideline for determining fluid deficits and maintenance requirements in the operating room. Fluid deficits should be replaced over the 1st 2 or 3 hr of intraoperative management. Deficits are generally calculated as the number of hours of NPO status multiplied by the hourly maintenance rate for the child. Half of this deficit is replaced during the 1st hr and half during each of the subsequent 2 hr. If hypotension or tachycardia occurs or persists in the early stages of anesthesia, more rapid replacement of the fluid deficit is indicated. The deficit is replaced with isotonic crystalloid solutions.

Third space losses are replaced with isotonic salt solutions. For large operations, such as abdominal or thoracic procedures, during which there may be a large amount of evaporative loss as well as a significant amount of third space loss, 8-10 mL/kg per hr of surgery is generally given as IV fluid replacement. For smaller operations, such as herniorrhaphy, pylonotomy, and minor procedures, fluid replacement at 3-5 mL/kg/hr is indicated for third space losses. Even when surgery involves the extremities and third space losses are minor, it is wise to give an additional 1-2 mL/kg/hr to replace them.

A crystalloid solution is indicated for blood loss, at 3 mL per mL of blood lost. This formula could be reduced somewhat if blood is replaced on an mL-per-ML basis with packed red blood cells or whole blood equivalent. The use of albumin or other suitable colloid, such as fresh-frozen plasma in neonatal surgery, also decreases the amount of crystalloid replacement needed for blood loss. During maintenance anesthesia, if large-volume transfusions are required, warming the blood and crystalloid solutions avoids hypothermia. With major surgery and the resultant systemic inflammatory response syndrome, capillary integrity is lost and third space losses are common. Failure to replace this third space loss and restore intravascular volume leads to hypotension, shock, acidemia, and renal failure, and further stimulates the systemic inflammatory response syndrome.

### RECOVERY FROM ANESTHESIA

Recovery from anesthesia includes emergence and postoperative recovery from surgery and anesthetics. Emergence describes the time and the physiologic response to decreasing depth of anesthesia during return to consciousness. During emergence, patients experience decreased anesthetic effect, increased stress responses, physiologic and psychologic responses to painful stimuli, excitement, and anxiety. Conscious realization of pain may lead to physiologic responses during emergence. Normal physiologic functions, such as spontaneous ventilation, resume and hemodynamic function improves. After routine elective procedures, the child should be fully conscious before leaving the operating room, with intact airway reflexes, the ability to follow simple commands, the effects of muscle relaxants reversed, and airway patency maintained. If the child is going to the ICU, or if for surgical reasons the decision is made to leave the child intubated, analgesia and sedation should be maintained, along with mechanical ventilation, in the postoperative period. Ideally, emergence should be as brief as possible, with maintenance of analgesia and anxiety and restoration of cardiorespiratory function. Inhalational anesthetic agents leave the system rapidly during ventilation, and muscle relaxants can be reversed; however, the effects of opioids, benzodiazepines, and IV hypnotic agents may be prolonged.

During emergence, the decision must be made whether to reverse the effects of muscle relaxants. The effects of long-acting, nondepolarizing muscle relaxants (vecuronium and pancuronium) are invariably reversed. If the child appears to be weak or to have respiratory depression in the postoperative phase, prolonged neuromuscular blockade should be considered.

### POSTANESTHESIA CARE UNIT

In the postanesthesia care unit (PACU), the child is observed until there is adequate recovery from anesthesia and sedation. Parents should be permitted to comfort their children in the PACU. Achievement of spontaneous breathing, adequate arterial saturation (>95%), and hemodynamic stability are key recovery end points. The child should be arousable, responsive, and oriented before discharge from the PACU. The amount of time spent in the PACU depends on whether the child is being discharged to an inpatient nursing unit, to an ICU, to a postrecovery area, or directly home. Discharge from the PACU depends on the child’s overall functional status—not merely the physiologic end points, but also the behavioral end points as well as the adequate provision of analgesia and control of postoperative nausea and vomiting. There are several scoring systems (Table 61-7) for determining whether a child is ready to be discharged from the PACU.

### Complications in the Postanesthesia Care Unit

#### Respiratory Depression

Prolonged emergence from anesthesia and respiratory depression can be caused by opioids or inadequate antagonism of neuromuscular blocking agents. Pain can cause significant hypoventilation, especially after thoracic or abdominal surgery. Delayed emergence from anesthesia can occur as a result of retention of inhaled anesthetic agents worsened by hypoventilation. Hypothermia, especially in neonates, delays metabolism and excretion of anesthetics and also aggravates neuromuscular blockade. If respiratory depression is profound, then maintenance of the airway may require an oral airway. If the depression is severe, endotracheal intubation and mechanical ventilation are indicated.

Only in rare cases, in which opioid suppression is suspected, is reversal of the effects of opioid with naloxone indicated. Opioid reversal with naloxone reverses not only the respiratory depression but also the analgesia. A somnolent child with respiratory depression may become excited, agitated in severe pain, uncontrollable, and/or hypertensive after naloxone. Opioid reversal necessitates bedside attention by the physician to monitor the child’s behavioral, hemodynamic, and respiratory status. Naloxone is shorter-acting than most opioid analgesics.

**Atelectasis** is another respiratory complication occurring in the 1st 48 hr after anesthesia. Although atelectasis suggests an inhaled foreign body, it is most likely caused by secretions and decreased respiratory effort secondary to pain. Microatelectasis may lead to postoperative infections. Aspiration pneumonia is another postoperative complication.

**Postoperative stridor** occurs in up to 2% of all pediatric patients. The use of uncuffed, atrumatic, nonirritant endotracheal tubes has decreased the incidence of airway trauma. The use of appropriately sized endotracheal tubes and assurance of an air leak <30 cm H₂O
pressure further decreases the risk of airway trauma. A history of stridor increases the likelihood of postoperative complications. Stridor may be severe enough after extubation to require reintubation. Retractions and respiratory distress in the postoperative period should suggest this complication, and stridor or wheezing should confirm the diagnosis. Racemic epinephrine aerosols are effective therapy; their use requires prolonged observation because of the potential for recurrence of the airway obstruction. Stridor in infants suggests the need for overnight observation.

Hemodynamic instability is much less common in the PACU. Volume expansion may be required to maintain adequate blood pressure, peripheral perfusion, and urine output. Requirement for excessive volume replacement (>30 mL/kg) to maintain blood pressure, perfusion, and urine output in the postoperative period is an indication of shock and occult bleeding, and it necessitates surgical consultation.

**Emergence delirium** is noted in <3% of children and is more common in those 3–9 yr old. In the immediate hour after surgery, children may become extremely restless, combative, and disoriented, and may be screaming, inconsolably crying, or poorly communicative. These children pose a danger to themselves. This phenomenon is more common when barbiturates are used as part of premedication or induction and inhalational anesthetics or ketamine forms part of the maintenance anesthetic. Although disorientation is common in the postanesthetic stage, erratic, delirious behavior requires attention, with gentle restraint, a quiet environment, and comforting. Potential postoperative complications, such as hypoglycemia and hypoxemia, should be ruled out. Occasionally, it is necessary to sedate the child with benzodiazepines, although these agents prolong postanesthesia recovery time and when they wear off, emergence delirium may recur.

### Awareness During Anesthesia
A primary goal of anesthesiology is obtunding consciousness to ablate awareness during procedures and recall afterward. In adults, certain anesthetic techniques are associated with an unacceptably high incidence of recall during anesthesia. Awareness and recall of events during a surgical procedure can be unpleasant and terrifying; the long-term sequelae of such recall in children are unknown. Continuous monitoring of cerebral electroencephalographic function by monitoring of the bispectral index has been recommended. Unfortunately, data in children do not confirm the efficacy of bispectral index monitoring as a means of determining anesthetic depth, and this fact, combined with the absence of meaningful data on intraoperative awareness and recall in infants and children, does not currently support the routine use of bispectral index monitoring.

### Postoperative Nausea and Vomiting
After general anesthesia, 40–50% of children may experience nausea and vomiting. More than 80% of all high-risk children receiving inhalational anesthesia experience postoperative nausea and vomiting (PONV). It may occur in the immediate postoperative period, within the 1st 1–2 hr, or several hours after surgery and anesthesia. The etiology may be related to the stress and trauma of surgery combined with the emetic effects of anesthetic agents. Pain is an important cause of nausea and vomiting. Opioid analogs also induce nausea and vomiting. Preoperative fasting does not decrease the incidence of nausea and vomiting. Indeed, hydration and glucose supplementation appear to be important factors in decreasing PONV. The use of analgesics other than opioids (acetaminophen, ketorolac) and regional or local anesthesia is associated with decreased PONV.

This complication prolongs recovery room times, requires significant nursing attention, and increases the use of potent antiemetic agents (ondansetron, other serotonin antagonists). Ondansetron is very efficacious as a prophylactic and in the treatment of PONV. Ondansetron and other serotonin antagonists are recommended for high-risk patients (strabismus surgery) or for actual treatment of PONV. They are contraindicated in children taking serotonin reuptake inhibitors for migraine headaches. Metoclopramide is useful prophylactically. Droperidol (which has an FDA-required black box label warning) must be used with caution because of the rare occurrence of prolonged QT interval and ventricular arrhythmias associated with its use.

### Thermoregulation and Malignant Hyperthermia
For patients in the PACU, thermoregulation remains abnormal for several hours. Shivering is common in the postoperative state, and a feeling of extreme cold is common. Warm blankets are very comforting and seem to decrease shivering. **Hyperthermia**, especially in neonates, leads to hypotension, bradycardia, acidosis, apnea, and prolongation of the effect of opioids and neuromuscular blocking agents. Although hyperthermia has deleterious effects, rewarming must be done cautiously to avoid burning and cutaneous hyperthermia. **Hyperthermia**, with temperatures in excess of 39°C (102.2°F), is of concern in the postoperative period. If it occurs within hours of the use of an inhalational anesthetic, especially if succinylcholine was used, malignant hyperthermia must be suspected.

**Malignant hyperthermia** is an acute hypermetabolic syndrome that is triggered by inhalational anesthetic agents and succinylcholine. It resembles neuroleptic malignant syndrome. The onset of malignant hyperthermia may be acute, and its course may be fulminating and rapidly fatal. This condition, albeit rare (approximately 1 in 60,000 pediatric patients given anesthesia) is a constant concern. The disease is familial, and a family history of death or a febrile reaction during anesthesia should alert the anesthesiologist to its potential. Its clinical course is characterized by rapid onset of fever, acidosis, hypercarbia, and increased expired CO₂. High fever (38.5–46.0°C [101.3–114.8°F]),
rising 1°C [1.8°F] every 5 min), muscle rigidity, metabolic acidosis, and hemodynamic collapse can occur. Death ensues from shock and cardiac dysrhythmias with ventricular fibrillation that is unresponsive to treatment. The mortality rate for malignant hyperthermia was once >70%. Aggressive therapy, including discontinuation of all inhalational anesthetic administration, correction of the metabolic acidosis, and treatment with the muscle relaxant sodium dantrolene, has reduced the mortality rate to <5%. Dantrolene and a kit containing supplies necessary to treat malignant hyperthermia should be present at every site where pediatric anesthesia is provided.

Malignant hyperthermia is probably genetically heterogeneous, with more than 10 genes contributing to susceptibility. Genetic mutations in the ryanodine receptor (the calcium channel of the sarcoplasmic reticulum) have been reported in 20-40% of humans with malignant hyperthermia. Certain myopathies are associated with the risk of malignant hyperthermia; these include Duchenne muscular dystrophy, Noonan phenotype, and, in children with a history of pttosis, squint, scoliosis, and muscle cramping. It is wise to avoid the use of succinylcholine in children with myopathies.

Malignant hyperthermia appears to occur from a massive triggering of excitation contraction coupling, sarcocelmal calcium release, and propagation of contraction by a complex biochemical process. The prolonged ischemic contraction leads to myolysis, with release of myoglobin, very high serum creatine phosphokinase levels, and renal failure secondary to myoglobinuria. Malignant hyperthermia generally occurs within the 1st 2 hr of anesthesia, but (rarely) can occur up to 24 hr later.

Certain phenomena are clues to the risk of malignant hyperthermia. The occurrence of masseter spasm during induction, with rigid clenching of the masseter muscles and an inability to open the mouth, may presage full-blown disease. Acute myoglobinuria associated with a malignant hyperthermia triggering agent is another clue. The child may not be hypermetabolic or febrile, but may have dark urine and high serum creatine phosphokinase levels, with the risk of myoglobin-induced renal tubular damage. The finding of dark urine after administration of an anesthetic requires investigation for malignant hyperthermia. An elevated creatine phosphokinase value and hemopositive urine in the absence of red blood cells in the urine indicate a need for renal protection with mannitol and alkaline diuresis.

Rapid therapy is essential. All known triggering agents must be stopped. Intravenous administration of dantrolene sodium (2.5 mg/kg IV as an initial dose) is begun as soon as possible. The need for repeated doses is indicated by the persistence of muscle rigidity, acidosis, and tachycardia, up to a maximum dose of 10 mg/kg. Once the symptoms are controlled, the patient should be observed for at least 24 hr after the laboratory values have returned to normal, because relapse can occur.

Prevention of malignant hyperthermia in susceptible patients requires the avoidance of triggering agents, which include inhalational anesthetics. Most anesthesiology departments are capable of delivering general anesthetics using anesthesia machines from which all traces of anesthetic vapors have been removed. Intravenous anesthesia and a nitrous-oxide technique are safe. Dantrolene prophylaxis is not recommended because the disease is rapidly treatable and because the drug causes respiratory depression and muscle weakness. For a child in whom malignant hyperthermia is suspected, the malignant hyperthermia hotline, 1-800-MHHYPER (1-800-644-9737), should be used to notify the Malignant Hyperthermia Association of the United States (MHAUS). The Malignant Hyperthermia Association registers susceptible patients and provides diagnostic and therapeutic information. Preanesthesia susceptibility testing includes genetic analysis of the ryanodine receptor gene, muscle biopsies, in vitro contraction studies, and, possibly, measurement of muscle CO2 production in response to intramuscular caffeine.

Postoperative Apnea
Apnea within the 1st 48 hr after surgery and anesthesia in premature infants is common; both central apnea and obstructive apnea (mixed apnea) may occur. The use of respiratory depressants may impair respiratory control in neonates. Apnea is also a recognized stress response in neonates, and inadequate anesthesia is associated with increased apnea and respiratory complications.

The risk of postoperative apnea in premature neonates is inversely proportional to postconceptual age at the time of surgery. This risk is minimal by the time premature infants have reached the postconceptual age of 60 wk. Apnea is most common within the 1st 12 hr after surgery; postanesthetic apnea has been reported in premature infants up to 48 hr later. The incidence of apnea in full-term infants is debatable and has not been clearly demonstrated. It is generally agreed that general anesthesia should be avoided, except for emergency surgery, in full-term children younger than 44 wk postconceptual age. If surgery is required within the 1st mo of life, overnight observation and monitoring are indicated. Theophyllines decrease the incidence of postoperative apnea; they do not ablate it and therefore are not routinely used. The safest course is to monitor premature infants younger than 60 wk postconceptual age and full-term infants younger than 1 mo for at least 24 hr after anesthesia.

PREANESTHETIC EVALUATION
Most previously healthy children require minimal preoperative assessment. The American Society of Anesthesiologists (ASA) classification system for anesthetic care is the American Society of Anesthesiologists Physical Status classification (Table 61-8).

For American Society of Anesthesiologists Physical Status 1 patients, a brief history, notation of medical allergies, and a physical examination focusing on the airway, lungs, and cardiac function are sufficient. For all children who are being assessed for anesthesia risk, a family history should be obtained, for reactions to anesthetics, for drug allergies, and for sudden intraoperative death or hyperthermia after surgery, which may indicate a risk of malignant hyperthermia. In previously anesthetized children, questions should be asked regarding intraoperative anesthetic complications. The history should focus on determining whether the child is at risk for anesthetic or surgical stress as well as cardiorespiratory disease and airway compromise.

Recent URIs should be noted. A URI is an upper respiratory illness associated with fever, mucopurulent green or yellow nasal discharge, productive cough, injected sclerae, and increased mucous secretions. Clear rhinorrhea is generally not a concern. URIs can increase airway reactivity for up to 6 wk in both normal children and children with a history of reactive airway disease. URIs can also increase the risk of laryngospasm and bronchospasm, reduce mucociliary clearance, and raise the risk of intraoperative atelectasis and hypoxemia. It is generally recommended to avoid general anesthesia for elective procedures for 4-6 wk after a URI. In patients with chronic sinusitis and nasal polyps, infection should be thoroughly treated before elective anesthesia.

Acute, fatal bronchospasm can occur during induction of anesthesia and endotracheal intubation for routine, minor surgery in children with asthma. Those children at particular risk for anesthetic complications with asthma are those who were (1) admitted to the hospital within the previous year for their asthma, (2) seen in an emergency department in the last 6 mo, (3) admitted to an ICU, or (4) treated with

<table>
<thead>
<tr>
<th>Table 61-8</th>
<th>American Society of Anesthesiology Physical Status Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1: Healthy patient, no systemic disease</td>
<td></td>
</tr>
<tr>
<td>Class 2: Mild systemic disease with no functional limitations (mild chronic renal failure, iron deficiency anemia, mild asthma)</td>
<td></td>
</tr>
<tr>
<td>Class 3: Severe systemic disease with functional limitations (hypertension, poorly controlled asthma or diabetes, congenital heart disease, cystic fibrosis)</td>
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</tr>
<tr>
<td>Class 4: Severe systemic disease that is a constant threat to life (critically and/or acutely ill patients with major systemic disease)</td>
<td></td>
</tr>
<tr>
<td>Class 5: Moribund patients not expected to survive 24 hr, with or without surgery</td>
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</tr>
</tbody>
</table>

Additional classification: “E”—emergency surgery

Airway Evaluation

Because the induction of anesthesia is associated with loss of spontaneous ventilation and airway reflexes, predicting the inability to bag-and-mask ventilate or endotracheally intubate a child before anesthesia is critical. The anesthesiologist must be told if the child has congenital anomalies that affect the airway (Table 61-9). Such anomalies include micrognathia syndromes, macrognathia syndromes, and some thoracic anomalies. Congenital anomalies associated with airway compromise should be diagnosed preoperatively. Conditions that impair mouth opening (temporomandibular joint disease) should be noted. A history of wheezing or stridor may indicate postoperative airway complications and difficult intraoperative airway management.

Mediastinal Masses

Children with anterior mediastinal masses, such as lymphomas and primary mediastinal tumors, are at serious risk for airway compromise, cardiac tamponade, and vascular obstruction. Induction of general anesthesia and even mild sedation can lead rapidly to total loss of the airway, with inability to ventilate the child and cardiovascular collapse. These patients often present in a semiemergency fashion, with the need for both a tissue diagnosis of the mass before treatment is initiated and a surgically placed central venous line.

Significant compression of vital structures can occur with seemingly mild symptoms. Tachypnea, orthopnea, wheezing, and sleep disturbances or avoidance of prone or supine positions are significant indicators of serious risk. Pericardial tamponade or superior vena cava syndromes are more concerning findings. A CT scan showing >50% compression of the airway at the carina is an indication to prohibit general anesthesia and provide only mild sedation. Echocardiographic or CT evidence of pericardial tamponade, right ventricular compression, or compression of the pulmonary artery suggests severe risk.

Table 61-9 Difficult Airway Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
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<tbody>
<tr>
<td>Achondroplasia</td>
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<tr>
<td>Airway tumors, hemangiomas</td>
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<tr>
<td>Apert syndrome</td>
</tr>
<tr>
<td>Beckwith-Wiedemann syndrome</td>
</tr>
<tr>
<td>Choanal atresia</td>
</tr>
<tr>
<td>Cornelia de Lange syndrome</td>
</tr>
<tr>
<td>Cystic hygroma/teratoma</td>
</tr>
<tr>
<td>DiGeorge syndrome</td>
</tr>
<tr>
<td>Fractured mandible</td>
</tr>
<tr>
<td>Goldenhar syndrome</td>
</tr>
<tr>
<td>Juvenile rheumatoid arthritis</td>
</tr>
<tr>
<td>Mucopolysaccharidosis</td>
</tr>
<tr>
<td>Pierre Robin syndrome</td>
</tr>
<tr>
<td>Smith-Lemli-Opitz syndrome</td>
</tr>
<tr>
<td>Treacher-Collins syndrome</td>
</tr>
<tr>
<td>Trisomy 21</td>
</tr>
<tr>
<td>Turner syndrome</td>
</tr>
</tbody>
</table>

Biopsy with the child under local anesthesia may be indicated. If anesthesia is required, cardiopulmonary bypass should be considered, in case it becomes impossible to ventilate the child during surgery. In high-risk children, consideration should be given to initiating treatment with steroids, radiation therapy, and chemotherapy before obtaining a tissue diagnosis.

Down Syndrome

Children with Down syndrome are occasionally behaviorally difficult and are especially fearful of medical caregivers (see Chapter 81). Their cardiac anomalies, macrognathia, and upper airway obstruction can be challenging. Children with Down syndrome have atlantoaxial instability due to odontoid hypoplasia and joint laxity (see Chapter 680.3). In younger children, extension of the neck, routinely used to maintain and intubate the airway, may lead to cervical dislocation and spinal cord trauma. Some anesthesiologists recommend extension and flexion lateral neck films to detect instability before anesthesia. In children with Down syndrome, it is wise to exercise caution in stabilizing the cervical spine and also to avoid cervical flexion and extension.

Cardiovascular System

Because of the depressant effects of anesthetics and the increased metabolic demands of surgery, any compromise of myocardial function should be clearly delineated preoperatively. A preoperative electrocardiogram, an echocardiogram, and a cardiology consultation are indicated for children with a history of heart disease. An intracardiac shunt will affect oxygenation status intraoperatively. Because of the significant effect on the oxygen supply-and-demand relationship caused by general anesthesia and surgical stress, obstructive lesions, such as a valvular stenosis, must also be clearly defined. A history of cardiac dysrhythmias should be clearly understood, because inhalational anesthetics are dysrhythmogenic.

In neonates, ductus arteriosus, myocardial compromise, pulmonary edema, or congenital heart disease can significantly complicate oxygen delivery during anesthesia. Accurate diagnosis of cardiac murmurs in neonates is essential. Any preoperative cardiovascular compromise will be worsened intraoperatively and can catastrophically complicate the perioperative course.

Anemia should be diagnosed and corrected preoperatively if possible. A hematocrit value >30% is generally acceptable for routine elective anesthesia. If there are reasons to expect significant blood loss or prolonged convalescence, anemia should be corrected preoperatively. In the emergency setting, transfusion may be required. Although lower hematocrit values can be tolerated in unstressed children, the significant threat to oxygen delivery posed by anesthesia and surgery, especially if blood loss is expected, requires maintenance of an adequate hemoglobin concentration perioperatively.

Evidence of coagulopathy should be sought. Easy bruising, the use of aspirin, and familial bleeding disorders should be discussed. Intraoperative hemorrhagic bleeding can be difficult to control; massive perioperative blood transfusions have significant risk of morbidity and mortality. Preoperative correction of coagulopathic disorders is indicated. In neonates, assurance of vitamin K prophylaxis and adequate coagulation status is critical before any significant surgery. In neonates and critically ill children, adequacy of platelet count and, where indicated, coagulation factors, prothrombin time, and partial thromboplastin time should be assured.

Neurobehavioral Considerations

Seizures, significant neurologic impairment, altered level of consciousness, respiratory airway compromise secondary to neurologic disease, and neuromuscular disease should be sought and evaluated. Anticonvulsant drug metabolism is often altered perioperatively, and this change may affect anticonvulsant drug levels. Anticonvulsants may also complicate anesthetic management. Maintenance of appropriate anticonvulsant therapy postoperatively is important to avoid new seizures. Cerebrospinal fluid secretion is increased during surgery and general anesthesia. This fact is significant in patients in whom elevated intracranial pressure is suspected and in children with ventriculoperitoneal
shunts. In infants or older children with ventriculoperitoneal shunts, shunt patency and function should be assured before surgery.

Illness and the need for surgery or painful medical procedures are psychologically traumatic events for children and their families. Children are also remarkably adept at sensing stressful signals from their parents and caregivers. Many children who require anesthesia may have significant levels of fear and anxiety. Most children undergoing surgery have new-onset negative behavioral changes in the postoperative period, such as maladaptive behavioral responses that include generalized anxiety, enuresis, enhanced separation anxiety, temper tantrums, nighttime crying, and fear of strangers, doctors, and hospitals. Approximately 20% show these negative behavioral adaptations for 6 mo after surgery. Sleep quality is also altered postoperatively, resulting in further behavioral compromise.

The risk factors for postoperative behavioral changes include preoperative or induction anxiety and behaviors indicating extreme stress, as well as emergence excitation. The type of surgery may be important, with tonsillectomy and genitourinary surgery having a high incidence of postoperative behavioral changes, whereas simple procedures (tympanostomy tubes) seem to be associated with fewer changes. Another risk factor is recurrent procedures, such as anesthesia for laser surgery, strabismus surgery, or repeated eye examinations, which lead to difficult behavioral changes and have a significant effect on family dynamics.

Preoperative psychologic preparation programs decrease the incidence of postoperative behavioral changes, which last for up to 1 mo. PPI does not improve postoperative behavior. Oral midazolam (0.5 mg/ kg) may decrease negative behavioral changes after surgery. Midazolam has the benefit of providing not only rapid-onset anxiolysis in 10-20 min but also very effective and rapid (10 min) amnesia.

Preoperative Preparation
The child should be in the best possible nutritional state, and nutritional supplementation, even hyperalimentation in chronically ill children, may be worthwhile.

Preoperative Fasting
Aspiration of gastric contents is a perioperative disaster and, if superimposed on lung disease, may be rapidly fatal. Aspiration may lead to laryngospasm and bronchospasm, with hypoxemia and hypoxic ischemic encephalopathy. It may also produce intraoperative atelectasis and postoperative pneumonia. It is vital to ensure that the stomach is as empty as possible before the induction of anesthesia. Acid aspiration is less likely with an empty stomach. Table 61-10 lists preoperative fasting (NPO status) guidelines.

![Table 61-10: Guidelines for Preoperative Fasting ("2-4-6-8 Rule")](https://example.com/table-61-10)

<table>
<thead>
<tr>
<th>TIME BEFORE SURGERY (hr)</th>
<th>ORAL INTAKE</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Clear, sweet liquids</td>
</tr>
<tr>
<td>4</td>
<td>Breast milk</td>
</tr>
<tr>
<td>6</td>
<td>Infant formula, fruit juices, gelatin</td>
</tr>
<tr>
<td>8</td>
<td>Solid food</td>
</tr>
</tbody>
</table>

*These are general guidelines and may differ among hospitals.

The Full Stomach
Because of the serious complications of aspiration of gastric contents, it is desirable to secure the airway as rapidly as possible after obtundation in patients at risk for having a full stomach. Gastric emptying may be delayed for up to 96 hr after an acute episode of trauma or surgical illness. Under these circumstances, induction of general anesthesia and endotracheal intubation are performed in a rapid sequence (rapid sequence induction; see Chapter 67).

The risks of rapid sequence induction include the possibility that if the airway cannot be intubated, the child is paralyzed without a protected airway and ventilation may be hazardous or impossible. Rapid sequence induction should be performed by those who can definitely achieve endotracheal intubation quickly. It should be avoided in patients with a history of failed oral endotracheal intubation or with any of the many syndromes (micrognathia) associated with difficult intubation. Under these circumstances, bronchoscopic awake intubation may be indicated.

Before rapid sequence anesthesia induction, the child should be preoxygenated by breathing 100% oxygen for 2 min to give an extra margin of safety if intubation is difficult. The child should not receive assisted ventilation either before or after the administration of drugs because this may lead to increased gastric air and actually increase the likelihood of vomiting, regurgitation, and aspiration.

One common regimen for rapid sequence induction includes the administration of 1.5-3 mg/kg of propofol concurrently with either 0.9-1.2 mg/kg of rocuronium or 1.5 mg/kg of vecuronium. Immediately after the administration of sedation and muscle relaxants, the Sellick maneuver (cricoid pressure) should be performed by applying firm pressure in a posterior direction against the cricoid cartilage. This displaces the cricoid cartilage into the esophagus, forming an artificial sphincter to prevent reflux of the gastroesophageal contents. Cricoid pressure should be maintained until correct placement of the endotracheal tube is verified by direct visualization, fogging of the tube, and, in all circumstances, positive end-tidal CO2.

**POSTOPERATIVE PAIN MANAGEMENT**
Continuation of analgesia and anxiolysis should follow surgery or painful procedures (see Chapter 62). Complete freedom from pain is not possible. Preoperative education about the surgery and a pain management plan, development of skills designed to decrease anticipatory anxiety, and active participation in treatment planning can be helpful for some children and families. Adjunctive therapy, such as virtual reality, hypnosis, pet therapy, and play therapy, also can decrease the need for potent analgesics postoperatively.

The combination of opioid and nonopioid analgesic agents and an understanding of the benefits and risks provide the foundation of pain management. A judicious combination of nonsteroidal antiinflammatory drugs, cyclooxygenase-2 inhibitors, intravenous acetaminophen, opioids, and regional analgesia has a role in postoperative pain management. Repeated evaluation is as important as the modality of pain management. Continuous and repetitive small doses of analgesia around the clock are more effective at reducing pain than occasional prn dosing intervals.

Patient-controlled analgesia (PCA), nurse-controlled analgesia, and parent-controlled analgesia are all used postoperatively (see Chapter 62). PCA provides continuous pain treatment and self-medication (vs intermittent or prn pain control) as well as control and comfort in an otherwise personally uncontrolled circumstance. PCA provides both a background low-dose infusion rate of a continuous opioid and the opportunity to supplement analgesia with bolus doses as needed. The practitioner can determine the continuous infusion rate, the bolus dose, the lockout interval, and the number of boluses per unit time that the patient may receive. PCA relies on the theory that patients cannot or will not overdose themselves because somnolence will decrease repeated self-administration. In young children, the use of the pain button (for pain relief) may be more difficult to ensure; children as young as 5 yr old have been able to use PCA successfully. In older children and adolescents, PCA should be a standard modality of postoperative pain management.
Regional Anesthesia

Regional anesthesia is the use of anesthetics to block the conduction of afferent neural impulses to the central nervous system. These can be local analgesic techniques, peripheral nerve blocks, nerve plexus blocks, or epidural and subarachnoid (spinal) nerve blocks. They may be administered either through a single injection (single shot) or through continuous infusion, as is common with epidural and occasionally subarachnoid blocks. They may be used for intraoperative anesthesia and postoperative analgesia, and they have the potential to decrease intraoperative analgesia and anesthetic use, as well as to provide postoperative pain management. Increased use of regional indwelling catheters to deliver continuous analgesia has shortened recovery times and hospital stays in children.

Analgesia at the site of need, without central cardiorespiratory depressant effects, can be valuable. Local anesthesia, with injection of lidocaine or bupivacaine into the affected area, can provide procedural analgesia that lasts for several hours. Infiltration of the wound site and the edges of an incision decreases postoperative pain in the initial hours after surgery. This can be performed by the surgeon at the conclusion of surgery and may supplement postoperative analgesia.

Epidural analgesia is common in pediatric practice. The epidural space lies between the dura and the pia and arachnoid membranes, an area through which all nerve roots pass. Bathing these nerve roots in local anesthetics inhibits conduction of pain impulses centrally. A single dose of epidural anesthetic may provide hours of pain relief, and a continuous infusion may provide effective pain relief for hours to days. The epidural injection of opioids can provide analgesia for 12-24 hr and is a potential supplement to postoperative analgesia.

A lumbar epidural injection is placed in the lumbar area to provide analgesia for labor and for surgery below the thorax. Caudal epidural analgesia is placed through the sacral hiatus, inferior to the distal end of the spinal cord. This is the site most commonly used for regional anesthesia and analgesia in children and is efficacious for the provision of pelvic and lower limb anesthesia as well as beneficial in orthopedic and urologic surgery. A continuous infusion of bupivacaine is the most common means of providing postoperative epidural pain relief; it may be mixed with an opioid (fentanyl or preservative-free morphine). It is also possible to provide epidural PCA with a continuous infusion pump and the ability of the patient to self-medicate with bolus prn dosing. Epidural analgesia can also provide pain relief in patients with chronic pain or pain caused by advanced malignant conditions.

The most serious complications of neuraxial anesthesia include respiratory depression, paralyzation of respiratory muscles, and, in extreme cases, brainstem analgesia and depression. The most common complications of neuraxial analgesia include mild discomfort; a paresthesia-like feeling of numbness and tingling; pruritus, which, if opioids are used, can be quite distressing; and occasional nausea and vomiting. Infection and epidural hematoma are extremely rare. Neuraxial opioids, especially when administered intrathecally, can cause respiratory depression; their use requires postoperative monitoring. The use of neuraxial opioids often requires treatment with antipruritic as well as antiemetic drugs.

Bibliography is available at Expert Consult.

61.1 Sedation and Procedural Pain

Randall C. Wetzel

The same drugs that induce general anesthesia are often used to provide sedation (see Table 61-5). Sedation care requires a presedation evaluation, intraprocedural monitoring, and postsedation recovery, analogous to the provision of anesthesia. Sedation is on the continuum between wakefulness and general anesthesia (see Table 61-4). The term conscious sedation refers to a condition in which a patient is sleepy, comfortable, and cooperative but maintains airway-protective and ventilatory reflexes. Unfortunately, for most children, this level of sedation provides little or no analgesia, and both psychologic and physiologic responses to painful stimuli persist. Sedation that is sufficient to obtund painful responses is most likely deep sedation. Deep sedation is a state of unarousability to voice and is accompanied by suppression of reflex responses. Management of sedated children requires vigilance and knowledge to ensure their safety and is governed by the same guidelines as anesthesia care (Table 61-11). A dose of sedative medication that causes minimal sedation in one subject may produce complete unconsciousness and apnea in another. Careful attention to guidelines for appropriate monitoring and management of sedation in children is imperative. For threatening and nonpainful procedures, anxiolysis or light sedation is frequently sufficient. For painful procedures (e.g., bone marrow aspiration, insertion of percutaneous IV catheter lines, lumbar punctures), the combination of sedation with analgesia that is required in children produces deep sedation.

Many specialists provide sedation and anesthesia care for children. The use of anesthetic agents is not limited to anesthesiologists, but a hospital’s department of anesthesiology provides expertise in developing and managing systems of anesthesia care, including sedation. With the widespread use of the deceptively safe general anesthetic agent propofol to provide sedation, hospitals, pediatricians, and other care providers must ensure that credentialing, oversight, quality assurance, and protocols for administration of anesthetic agents provide safe care. Involvement of anesthesiologists in organizing services, training other practitioners, overseeing safety, systems, and quality, and remaining involved in the delivery of such care is sound practice. The elements of a safe system to provide procedural sedation for children are as follows:

- Defining the required knowledge set
- Defining the required skill set
- Determining the appropriate requisite training
- Ensuring adequate understanding of the drugs and their effects (desired and undesired) and interactions
- Credentialing providers
- Ensuring ongoing maintenance of skills
- Reviewing the practice
- Ensuring that the sites where anesthesia care is provided meet recognized standards
- Last but not least, overseeing a process of continuous quality improvement

Sedation with chloral hydrate (not approved by the FDA in the United States or the European Medicines Agency in the European Union), pentobarbital, or benzodiazepines is often adequate for nonpainful procedures. Nevertheless, there can be a high failure rate as well as complications by using this method, such as prolonged sedation (hours to overnight), ataxia, nausea and vomiting, desaturation, and the occasional need for rapid intervention. The temptation to add opioids and deepen sedation increases the risk of complications. The use of dexmedetomidine for procedural sedation is safe; recovery time can be prolonged, and success can be variable. The quickest way to ensure safely reversible sedation is with potent anesthetic agents.

### Table 61-11: Systematic Approach to Sedation in Children

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documentation of vital signs and condition on a time-based record</td>
<td>Thorough medical history, anticipating underlying medical problems</td>
</tr>
<tr>
<td>Emergency backup system, “code” team, and “crash cart”</td>
<td>Careful physical examination focused on the cardiorespiratory system and</td>
</tr>
<tr>
<td>Discharge criteria documenting recovery from sedation</td>
<td>airway</td>
</tr>
<tr>
<td>Fully equipped and staffed recovery area</td>
<td>Appropriate fasting</td>
</tr>
<tr>
<td>Appropriate sized equipment</td>
<td>Informed consent</td>
</tr>
<tr>
<td>Pediatric drug dosing (mg/kg)</td>
<td>A separate, dedicated observer to monitor sedated patients who may have</td>
</tr>
<tr>
<td>Appropriate fasting</td>
<td>have airway compromise (induced or preexisting)</td>
</tr>
<tr>
<td>Informed consent</td>
<td>Documentation of vital signs and condition on a time-based record</td>
</tr>
<tr>
<td>Reviewing the practice</td>
<td>Emergency backup system, “code” team, and “crash cart”</td>
</tr>
<tr>
<td>Ensuring that the sites where anesthesia care is provided meet recognized standards</td>
<td>Fully equipped and staffed recovery area</td>
</tr>
<tr>
<td>Ensuring ongoing maintenance of skills</td>
<td>Discharge criteria documenting recovery from sedation</td>
</tr>
<tr>
<td>Ensuring that the sites where anesthesia care is provided meet recognized standards</td>
<td></td>
</tr>
</tbody>
</table>
Bibliography
The ultra–short-acting anesthetics (propofol, methohexital, remifentanil) provide effective procedural sedation, but their use carries a higher likelihood of inadvertent oversedation and induction of general anesthesia. These anesthetics offer efficient and rapidly reversible procedural sedation. However, their use requires the presence of an anesthesiologist and/or specially trained, experienced, and qualified physicians.

Bibliography is available at Expert Consult.

61.2 Anesthetic Neurotoxicity

Randall C. Wetzel

There is compelling experimental evidence that anesthesia-induced neurodegeneration with developmental impairment occurs in neonatal animals. Pediatric anesthesiologists have become deeply concerned by the demonstration of anesthetic-induced apoptotic neuronal cell death, central nervous system neurodegenerative changes, and their effects on the developing brain. These studies demonstrate both histopathologic changes and developmental defects from both inhalational and IV anesthetics, including isoflurane, ketamine, benzodiazepines, and propofol given to newborn animals. Combinations of drugs may cause more injury. Existing nonclinical data implicate both N-methyl-D-aspartate and γ-aminobutyric acid pathways in apoptosis and cell death in neonates.

The studies reporting these results were performed in animals (largely rodents), and great controversy exists concerning dose, duration of treatment, species differences, and experimental design. Although there is cause for concern and further study, alternatives to general anesthesia for many procedures in infants do not exist. Perhaps regional anesthetic techniques and narcotic-based anesthetics will be increasingly used. Interestingly, dexmedetomidine appears to block the neurotoxic effects of other anesthetics. There is insufficient current data for suggesting the safety of one anesthetic approach over another. The potential for this neurotoxicity must be balanced against the necessity of providing adequate anesthesia for neonates.

Bibliography is available at Expert Consult.
Bibliography

Pain is both a sensory and an emotional experience that, when unrecognized and undertreated, extracts a significant physiologic, biochemical, and psychologic toll. Many disease processes and most interventional procedures in pediatrics are associated with pain.

DEFINITION AND CATEGORIES OF PAIN

Pain is defined by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." The important elements of this definition to be emphasized are (1) pain encompasses both peripheral physiologic and central cognitive/emotional components and (2) pain may or may not be associated with ongoing tissue damage—pain may exist in the absence of demonstrable somatic pathology, and may rather be the acquired or genetic consequence of abnormalities of peripheral neural signaling, central modulation, or brain processing of peripheral sensations or nociception.

Table 62-1 specifies important pain categories commonly treated (somatic, visceral, and neuropathic) and defines the elements and characteristics of nociception, the peripheral physiologic aspect of pain perception (Fig. 62-1). Nociception refers to how specialized fibers (largely, but not exclusively, the small unmyelinated A-delta and C fibers) in the peripheral nervous system transmit nerve impulses (usually transmitting signals originating from peripheral mechanoreceptors and chemoreceptors) through synapses in the spinal cord's dorsal horn through (but not exclusively through) the spinothalamic tracts to the brain's higher centers, where nociception is converted to pain, with all of its cognitive and emotional ramifications.

THE ASSESSMENT AND MEASUREMENT OF PAIN IN CHILDREN

Whenever feasible, the physician should ask the patient about the character, location, quality, duration, frequency, and intensity of the pain. Some children may not report pain because of fears (often well-founded) of talking to strangers, disappointing or bothering others, receiving an injection if they report pain, returning to the hospital if they admit to pain, and other negative possible reactions. For infants and nonverbal children, their parents, pediatricians, nurses, and other caregivers are constantly challenged to interpret whether the child's distressed behaviors represent pain, fear, hunger, or a range of other perceptions or emotions. Therapeutic trials of comfort measures (cuddling, feeding) and analgesic medications may be helpful in clarifying the triggers of the behaviors.

Behavior and physiologic signs are useful, but they can be misleading. A toddler may scream and grimace during an ear examination because of fear rather than pain. Conversely, children with inadequately relieved persistent pain from cancer, sickle cell disease, trauma, or surgery may withdraw from their surroundings and appear very quiet, leading observers to conclude falsely that they are comfortable or sedated. In these situations, increased dosing of analgesics may make the child become more, not less, interactive and alert. Similarly, neonates and young infants may close their eyes, furrow their brows, and clench their fists in response to pain. Adequate analgesia is often associated with eye opening and increased involvement in the surroundings. A child who is experiencing significant chronic pain may play normally as a way to distract attention away from pain. This coping behavior is sometimes misinterpreted as evidence of the child's "faking" or exaggerating pain at other times.

Age-Specific and Developmentally Specific Measures

Because infants, young children, and nonverbal children cannot express the quantity of pain they experience, several pain scales have been devised in an attempt to quantify pain in these populations (Fig. 62-2; Table 62-2).

The Newborn and Infant

There are several behavioral distress scales for the infant and young child, mostly emphasizing the patient's facial expressions, crying, and body movement. Facial expression measures appear most useful and specific in neonates. Autonomic and vital signs can indicate pain, but because they are nonspecific, they may reflect other processes, including fever, hypoxemia, and cardiac or renal dysfunction.

The Older Child

Children ages 3-7 yr become increasingly articulate in describing the intensity, location, and quality of pain. Pain is occasionally referred to adjacent areas; referral of hip pain to the leg or knee is common in this age range. Self-report measures for children this age include using drawings, pictures of faces, or graded color intensities. Children age 8 yr and older can usually use verbal numerical rating scales or visual analog pain scales accurately (see Fig. 62-2). Verbal numerical ratings are preferred and considered the gold standard; valid and reliable ratings can be obtained from children 8 yr and older. The Numerical
Rating Scale consists of numbers from 0-10, in which 0 represents no pain and 10 represents very severe pain. There is debate about the label for the highest pain rating, but the current agreement is not to use the term “worst pain possible,” because children can always imagine a greater pain. In the United States, regularly documented pain assessments are required for hospitalized children and children attending outpatient hospital clinics and emergency departments. Pain scores do not always correlate with changes in heart rate or blood pressure.

The Cognitively Impaired Child
Measuring pain in cognitively impaired children remains a challenge. Understanding pain expression and experience in this population is important, because behaviors may be misinterpreted as indicating that cognitively impaired children are more insensitive to pain than cognitively competent children. Children with trisomy 21 may express pain less precisely and more slowly than the general population. Pain in children with autism spectrum disorders may be difficult to assess because these children may be both hyposensitive and hypersensitive to many different types of sensory stimuli, and they may have limited communication abilities. Although self-reports of pain can be elicited from some children who are cognitively impaired, observational measures have better validation among these children. The Noncommunicating Child's Pain Checklist—Postoperative Version is recommended for children up to 18 yr. Maladaptive behaviors and reduction in functions may also indicate pain. Children with severe cognitive impairments frequently experience pain.

A CONCEPTUAL FRAMEWORK FOR THE TREATMENT OF PEDIATRIC PAIN
A number of models have been developed to understand the various factors that influence children's pain. Many of these theories focus on factors that explain the interindividual variability in pain perception, and the chronicity and impairment experienced with pain. Central to these models are interrelationships among biologic, cognitive, affective, and social factors that influence children's pain and disability, commonly referred to as biopsychosocial models of pain. Biologic factors include the child’s physical health, central nervous system factors (pain processing), sex, pubertal status, and genetic factors.

### Table 62-1 Pain Categories and Characteristics

<table>
<thead>
<tr>
<th>PAIN CATEGORY</th>
<th>DEFINITION AND EXAMPLES</th>
<th>CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatic</td>
<td>Pain resulting from injury to or inflammation of tissues (skin, muscle, tendons, bone, joints, fascia, vasculature, etc.) Examples: burns, lacerations, fractures, infections, inflammatory conditions</td>
<td>In skin and superficial structures: sharp; pulsatile; well-localized In deep somatic structures: dull; aching; pulsatile; not well-localized</td>
</tr>
<tr>
<td>Visceral</td>
<td>Pain resulting from injury to or inflammation of viscera Examples: angina, hepatic distention, bowel distention or hypermobility, pancreatitis</td>
<td>Aching and cramping; nonpulsatile; poorly localized (e.g., appendiceal pain perceived around umbilicus) or referred to distant locations (e.g., angina perceived in shoulder)</td>
</tr>
<tr>
<td>Neuropathic</td>
<td>Pain resulting from injury to, inflammation of, or dysfunction of the peripheral or central nervous systems. Examples: complex regional pain syndrome, phantom limb pain, Guillain-Barré syndrome, sciatica</td>
<td>Spontaneous; burning; lancinating or shooting; dyesthesias (pins and needles, electrical sensations); hyperalgesia (amplification of noxious stimuli); hyperpathia (widespread pain in response to a discrete noxious stimulus); allodynia (pain in response to nonpainful stimulation); pain may be perceived distal or proximal to site of injury, usually corresponding to innervation pathways (e.g., sciatica)</td>
</tr>
</tbody>
</table>

![Figure 62-1 The typical neural pathways of nociception, also showing higher projection of nociception to the cortex, where the sensation of nociception is translated to the conscious and emotional phenomenon of pain. DLPT, dorsolateral pontine tegmentum; PAG, periaqueductal gray; RF, reticular formation.](image)
Behavioral Indicators

Facial grimacing: The Neonatal Facial Coding System uses several facial actions that may be indicators of pain. Pain is characterized by a bulging brow with tight creases in between; tightly closed eyelids; a deeply furrowed nasolabial groove; a horizontal, wide opened mouth; and a taut tongue that may be quivering along with the chin.

Crying: May be an indicator of pain.

Activity: Withdrawal or immobilization of a limb may be an indicator of pain.

Response to comfort measures: Feeding, swaddling, holding, and ensuring that the infant is neither wet nor cold may help to discriminate between pain and other conditions.

Physiologic indicators: Alterations in heart rate, blood pressure, \( \text{SpO}_2 \), respiratory rate, or alterations in pattern of respiration may be nonspecific indicators of pain.

Multidimensional Instrument

**FLACC** Scoring System: May be used in preverbal, mechanically ventilated, or cognitively impaired patients; it is an acronym that includes five indicators, each scored as a 0, 1, or 2 that forms a ten-point composite scale with a range from "0" (no pain) to "10" (worst pain).

**FLACC**: Score each category between 0 and 2. The total score may be any number from 0 to 10.

<table>
<thead>
<tr>
<th>Score:</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face</td>
<td>No expression</td>
<td>Occasional action</td>
<td>Frequent action</td>
</tr>
<tr>
<td>Legs</td>
<td>Normal</td>
<td>Restless or tense</td>
<td>Kicking, legs withdrawn</td>
</tr>
<tr>
<td>Activity</td>
<td>Quiet</td>
<td>Shifting or tense</td>
<td>Rigid, arched, jerking</td>
</tr>
<tr>
<td>Cry</td>
<td>None</td>
<td>Moan, whimper</td>
<td>Steady crying, screaming, sobbing, or frequent complaints</td>
</tr>
<tr>
<td>Consolability</td>
<td>Content</td>
<td>Consolable</td>
<td>Inconsolable</td>
</tr>
</tbody>
</table>

Self-Report of Pain

Categorical description: Toddlers or young children are asked to say if they are having "a little bit," a "middle amount," or "a lot" of pain.

Faces Scales: Children who do not have an appreciation of ordinal numbering are asked to rate their pain based upon cartoons depicting facial indicators of distress.

NRS: Older children and teenagers are asked to rate their pain on a scale of "0" (no pain) to "10" (worst pain).

VAS: Children or teenagers are asked to move an indicator along a mechanical slide to depict the level of pain; the clinician reads a number along a 10-cm indicator on the back to determine the numeric score.


Individual child cognitive and affective factors related to perception of pain are anxiety, fear, negative affect, pain behaviors, and functional disability, whereas social factors include such areas as culture, socio-economic status, school environment, social and peer interactions, and parental and family factors.

A framework that considers the interplay of biologic, psychologic, and social factors is useful for understanding pediatric pain and to guide pain assessment and the delivery of both pharmacologic and nonpharmacologic interventions for pain management. Many simple interventions designed to promote relaxation and patient control can be expected to work synergistically with pain medications for optimal relief of pain and related distress. Moreover, psychologic interventions are often coupled with physical therapy interventions to assist in the management of disabling chronic pain.

Pharmacologic Treatment of Pain
Developmental Pharmacology

The pharmacokinetics and pharmacodynamics of analgesics vary with age; drug responses in infants and young children differ from those in older children and adults. The elimination half-life of most analgesics is prolonged in neonates and young infants because of their immature hepatic enzyme systems and glomerular filtration. Clearance of
analgesics may also be variable in young infants and children. Renal blood flow, glomerular filtration, and tubular secretion increase dramatically in the 1st few weeks, approaching adult values by 3-5 mo of age. Renal clearance of analgesics is often greater in toddlers and preschool-age children than in adults, whereas in premature infants clearance is reduced. Age-related differences in body composition and protein binding also exist. Total-body water as a fraction of body mass increases in neonates, particularly in the 1st few weeks, approaching adult values by 3-5 yr and older. In young children, body composition changes with advancing age; total body water decreases and percentage of body fat increases. Because of decreased serum concentrations of albumin and α1-acid glycoprotein, neonates have reduced protein binding of some drugs, resulting in higher amounts of free, unbound, pharmacologic or antiplatelet effects of aspirin and NSAIDs, making it a particularly useful drug in patients with cancer. Unlike aspirin and NSAIDs, acetaminophen has only mild antiinflammatory action.

Acetaminophen toxicity can result from either a large single dose or cumulative, excessive dosing over days or weeks (see Chapters 63 and 363). A single, massive overdose overwhelms the normal glucuronidation and sulfation metabolic pathways in the liver, whereas long-term overdosing exhausts supplies of the sulfhydryl donor glutathione, leading to alternative cytochrome P450–catalyzed oxidative metabolism and the production of the hepatotoxic metabolite N-acetyl-p-benzoquinone imine (NAPQI). Toxicity manifests as fulminant hepatic necrosis and failure in infants, children, and adults. Drug biotransformation processes are immature in neonates, very active in young children, and somewhat less active in adults. Young children are more resistant to acetaminophen-induced hepatotoxicity than are adults as a result of metabolism differences: Sulfation predominates over glucuronidation in young children, leading to a reduction in N-acetyl-p-benzoquinone imine production.

**Acetaminophen, Aspirin, Nonsteroidal Antiinflammatory, and Coxib Drugs**

Acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs) have replaced aspirin as the most commonly used antipyretics and oral, nonopioid analgesics (Table 62-3).

**Acetaminophen**, a generally safe, nonopioid analgesic and antipyretic, has the advantage of intravenous, rectal, and oral routes of administration. Acetaminophen is not associated with the gastrointestinal or antiplatelet effects of aspirin and NSAIDs, making it a

### Table 62-2 Pain Measurement Tools

<table>
<thead>
<tr>
<th>NAME</th>
<th>FEATURES</th>
<th>AGE RANGE</th>
<th>ADVANTAGES</th>
<th>VALIDATION AND USES</th>
<th>LIMITATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual Analog Scale (VAS)</td>
<td>Horizontal 10-cm line; subject marks a spot on the line between anchors of “no pain” (or neutral face) and “most pain imaginable” (or sad face)</td>
<td>6-8 yr and older</td>
<td>Good psychometric properties; validated for research purposes</td>
<td>Acute pain Surgical pain Chronic pain</td>
<td>Cannot be used in younger children or in those with cognitive limitations Requires language skills and numerical processing; upper anchor of “most pain” requires an experiential reference point that is lacking in many children</td>
</tr>
<tr>
<td>Likert Scale</td>
<td>Integers from 0-10, inclusive, corresponding to a range from no pain to most pain</td>
<td>6-8 yr and older</td>
<td>Good psychometric properties; validated for research purposes</td>
<td>Acute pain Surgical pain Chronic pain</td>
<td>Same as for VAS</td>
</tr>
<tr>
<td>Faces Scales (e.g., FACES-R, Wong-Baker, Oucher, Bier, McGrath scales)</td>
<td>Subjects rate their pain by identifying with line drawings of faces or photos of children</td>
<td>4 yr and older</td>
<td>Can be used at younger ages than VAS and Likert</td>
<td>Acute pain Surgical pain</td>
<td>Choice of “no pain” face affects responses (neutral vs smiling); not culturally universal</td>
</tr>
<tr>
<td>Behavioral or combined behavioral-physiologic scales (e.g., FLACC, N-PASS, CHEOPS, OPS, FACS, NIPS)</td>
<td>Scoring of observed behaviors (e.g., facial expression, limb movement) ± heart rate and blood pressure</td>
<td>Some work for any ages; some work for specific age groups, including preterm infants</td>
<td>May be used in both infants and nonverbal children</td>
<td>FLACC, N-PASS: Acute pain Surgical pain</td>
<td>Nonspecific; overrates pain in toddlers and preschool children; underrates persistent pain; some measures are convenient, but others require videotaping and complex processing; vital sign changes unrelated to pain can occur and may affect total score</td>
</tr>
<tr>
<td>Autonomic measures (e.g., heart rate, blood pressure, heart rate spectral analyses)</td>
<td>Scores changes in heart rate, blood pressure, or measures of heart rate variability (e.g., “vagal tone”)</td>
<td>All ages</td>
<td>Can be used at all ages; useful for patients receiving mechanical ventilation</td>
<td>Nonverbal</td>
<td>Nonspecific; vital sign changes unrelated to pain may occur, and may artifactualy decrease score</td>
</tr>
<tr>
<td>Hormonal-metabolic measures</td>
<td>Plasma or salivary sampling of “stress” hormones (e.g., cortisol, epinephrine)</td>
<td>All ages</td>
<td>Can be used at all ages</td>
<td>Nonverbal</td>
<td>Changes unrelated to pain can occur; inconvenient; cannot provide “real-time” information; standard normal values not available for every age bracket</td>
</tr>
</tbody>
</table>

**Chapter 62 ♦ Pediatric Pain Management**
### Table 62-3 Commonly Used Nonopioid Medications

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>DOSAGE</th>
<th>COMMENT(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>10-15 mg/kg PO q4h</td>
<td>Little antiinflammatory action; no antiplatelet or adverse gastric effects; overdosing can produce fulminant hepatic failure</td>
</tr>
<tr>
<td></td>
<td>10 mg/kg IV q4h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15 mg/kg IV q6h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 mg/kg IV q6h (&lt;2 yr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20-30 mg/kg/PR q4h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>40 mg/kg/PR q6-8h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximum daily dosing: 90 mg/kg/24 hr (children)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximum daily dosing: 60 mg/kg/24 hr (&lt;2 yr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximum daily dosing: 30-45 mg/kg/24 hr (neonates)</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>10-15 mg/kg PO q4h</td>
<td>Antiinflammatory; prolonged antiplatelet effects; may cause gastritis; associated with Reye syndrome</td>
</tr>
<tr>
<td></td>
<td>Maximum daily dosing: 120 mg/kg/24 hr (children)</td>
<td></td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>8-10 mg/kg PO q6h</td>
<td>Antiinflammatory; transient antiplatelet effects; may cause gastritis; extensive pediatric safety experience</td>
</tr>
<tr>
<td>Naprosyn</td>
<td>5-7 mg/kg PO q8-12h</td>
<td>Antiinflammatory; transient antiplatelet effects; may cause gastritis; more prolonged duration than that of ibuprofen</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>Loading dose 0.5 mg/kg, then 0.25-0.3 mg/kg IV q6h to a maximum of 5 days; maximum dose 30 mg loading with maximum dosing of 15 mg q6h</td>
<td>Antiinflammatory; reversible antiplatelet effects; may cause gastritis; useful for short-term situations in which oral dosing is not feasible</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>3-6 mg/kg PO q12-24h</td>
<td>Antiinflammatory; no antiplatelet or gastric effects; cross-reactivity with sulfa allergies</td>
</tr>
<tr>
<td>Choline magnesium salicylate</td>
<td>10-20 mg/kg PO q8-12h</td>
<td>Weak antiinflammatory; lower risk of bleeding and gastritis than with conventional NSAIDs</td>
</tr>
<tr>
<td>Nortriptyline, amitriptyline, desipramine</td>
<td>0.1-0.5 mg/kg PO qhs</td>
<td>For neuropathic pain; facilitates sleep; may enhance opioid effect; may be useful in sickle cell pain; risk of dysrhythmia in prolonged QTc syndrome; may cause fatal dysrhythmia in overdose; FDA says agents may enhance suicidal ideation</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>100 mg bid or tid titrated to up to 3,600 mg/24 hr</td>
<td>For neuropathic pain; associated with sedation, dizziness, ataxia, headache, and behavioral changes</td>
</tr>
<tr>
<td>Quetiapine, risperidone, chlorpromazine, haloperidol</td>
<td>Quetiapine: 6.25 or 12.5 mg PO qd (hs); may use q6h prn acute agitation with pain. Escalate dose to 25 mg/dose if needed. Risperidone: useful for PDD spectrum or tic disorder and chronic pain; 0.25-1 mg (in 0.25-mg increments) qd or bid; see PDR for other dosing.</td>
<td>Useful when arousal is amplifying pain; often used when patient first starting SSRI and then weaned after at least 2 wk; check for normal QTc before initiating; side effects include extrapyramidal reactions (diphenhydramine may be used to treat) and sedation; in high doses, can lower the seizure threshold</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>10-20 mg PO qd (usually in morning)</td>
<td>SSRI for children with anxiety disorders in which arousal amplifies sensory signaling; useful in PDD spectrum disorders in very low doses; best to use in conjunction with psychiatric evaluation</td>
</tr>
<tr>
<td>Sucrose solution via pacifier or gloved finger</td>
<td>Preterm infants (gestational age): 28 wk: 0.2 mL swabbed into mouth 28-32 wk: 0.2-0.2 mL, depending on suck/swallow &gt;32 wk: 2 mL  Term infants: 1.5-2 mL PO over 2 min</td>
<td>Allow 2 min before starting procedure; analgesia may last up to 8 min; the dose may be repeated once</td>
</tr>
</tbody>
</table>

FDA, U.S. Food and Drug Administration; IV, intravenously(ly); NSAIDs, nonsteroidal antiinflammatory drugs; PDD, pervasive developmental disorder; PDR, Physicians’ Desk Reference; PR, per rectum; QTc, corrected QT interval on an electrocardiogram; SSRI, selective serotonin reuptake inhibitor.

(found in gastric mucosa and platelets) and COX-2 (active in inflammatory pathways and cortical renal blood flow regulation) enzymes that synthesize prostaglandins. In children with juvenile idiopathic arthritis, ibuprofen and aspirin are equally effective, but ibuprofen is associated with fewer side effects and better drug adherence. NSAIDs and coxibs used adjunctively in surgical patients reduce opioid requirements (and, therefore, opioid side effects) by as much as 35-40%. Although NSAIDs can be useful postoperatively, they should be used as an adjunct to, not as a substitute for, opioids in patients with moderate to severe pain.

Ketorolac, an IV or intranasal NSAID, is useful in treating moderate to severe acute pain in patients who are unable or unwilling to swallow oral NSAIDs. Intravenous ibuprofen is approved in the United States for the management of pain and fever for 5 days or fewer, although there is no pediatric indication in the package labeling. In Europe, IV ibuprofen is used to treat pediatric pain.

Adverse effects of NSAIDs are uncommon, but they may be serious when they occur. They include loss of bone growth and healing; gastritis with pain and bleeding; decreased renal blood flow that may reduce glomerular filtration and enhance sodium reabsorption, in some cases leading to tubular necrosis; hepatic dysfunction and liver failure; inhibition of platelet function; and an increased incidence of cardiovascular events in patients predisposed to stroke and myocardial infarction. Although the overall incidence of bleeding is very low, gastric bleeding is the most common cause of mortality related to this class of analgesics.

NSAIDs should not be used in the child with a bleeding diathesis or at risk for bleeding or when surgical hemostasis is a concern, such as after tonsillectomy. The drug class is usually avoided in the setting of bone healing, except perhaps in the first few days following surgery.

Renal injury from short-term use of ibuprofen in euvolemic children is quite rare; the risk is increased by hypovolemia or cardiac...
dysfunction. The safety of both ibuprofen and acetaminophen for short-term use is well established (see Table 62-3).

Coxib drugs available in the United States are limited to oral celecoxib, whereas in Europe and elsewhere parenteral parecoxib and oral rofecoxib are available (parecoxib was not approved for use in the United States, while rofecoxib was approved and withdrawn from the market because of concern of enhancement of the risk of heart attacks and stroke, which was subsequently found to be associated with all the coxibs and NSAID drugs as well). The coxib drugs are selective COX-2 enzyme inhibitors; therefore they are effective antiinflammatory and analgesic molecules that generally do not result in platelet inhibition and bleeding or in gastric inflammation or ulceration, findings that may be seen with the nonselective COX inhibitors in the NSAID class. However, coxib drugs do inhibit regulation of cortical renal blood flow, and therefore carry the same risk of renal dysfunction and acute tubular necrosis. Celecoxib is therefore an appropriate primary or adjunctive analgesic to use in children following surgery, children with gastric mucosal pathology, or oncology patients in whom concern for hemostasis contraindicates conventional NSAIDs.

**Opioids**

Opioids are analgesic substances either derived from the opium poppy (opiates) or synthesized to have a similar chemical structure and mechanism of action (opioids). The older, pejorative term narcotics should not be used for these agents, because it connotes criminality and lacks pharmacologic descriptive specificity. Opioids are administered for moderate and severe pain, such as acute postoperative pain, sickle cell crisis pain, and cancer pain. Opioids can be administered by the oral, rectal, oral transmucosal, transdermal, intranasal, IV, epidural, intrathecal, subcutaneous, or intramuscular route. Historically, infants and young children have been underdosed with opioids for fear of significant respiratory side effects. In contrast, the use of opioids for moderate-to-severe noncancer pain does not have the evidence base that their use in cancer-associated pain does. There is concern for the potential for unwarranted use of opioids to increase the incidence of side effects. With proper understanding of the pharmacokinetic and pharmacodynamics of opioids, children can receive effective relief of pain and suffering with a good margin of safety (Tables 62-4 to 62-7).

Opioids act by mimicking the actions of endogenous opioid peptides, binding to receptors in the brain, brainstem, spinal cord, and peripheral nervous system, and thus leading to inhibition of nociception. Opioids have dose-dependent respiratory depressant effects, and they blunt ventilatory responses to hypoxia and hypercarbia. These respiratory depressant effects can be increased with coadministration of other sedating drugs, such as benzodiazepines or barbiturates. What was once thought to represent infants’ particular sensitivity to the opioids’ respiratory depressant effects we now understand to be a result of infants’ lower metabolic clearance of opioids and higher blood levels with frequent dosing.

Optimal use of opioids requires proactive and anticipatory management of side effects (see Table 62-6). Common side effects include constipation, nausea, vomiting, urinary retention, and pruritus. The most common, troubling, but treatable side effect is constipation. Stool softeners and stimulant laxatives should be administered to most patients receiving opioids for more than a few days. Constipation also remains a problem with long-term opioid administration. A peripherally acting opiate μ-receptor antagonist, methylnaltrexone, promptly and effectively reverses opioid-induced constipation in patients with chronic pain who are receiving opioids daily. In addition lubiprostone, an epithelial chloride channel agent, has been approved for the treatment of opioid-induced constipation in adults with chronic noncancer pain. The side effect of nausea typically subsides with long-term dosing, but it may require treatment with antiemetics, such as a phenothiazine, butyrophenones, antihistamines, or a serotonin receptor antagonist such as ondansetron or granisetron. Pruritus and other complications during patient-controlled analgesia (PCA) with opioids may be effectively managed by low-dose IV naloxone (see Table 62-6).

One of the potent barriers to effective management of pain with opioids is the unrealistic fear of addiction held by many prescribing pediatricians and parents. Pediatricians should understand the phenomena of tolerance, dependence, withdrawal, and addiction (see Table 62-5) and should know that the rational short- or long-term use of opioids in children does not lead to a predilection or risk of addiction in a child not otherwise at risk by virtue of genetic background and social milieu. It is important for pediatricians to realize that even patients with recognized substance-abuse diagnoses are entitled to effective analgesic management, which often includes the use of opioids. When there are legitimate concerns about addiction in a patient, then safe, effective opioid pain management is often best managed by specialists in pain management and/or addiction medicine.

There is no longer a reason to administer opioids by intramuscular injection. Continuous IV infusion of opioids is an effective option that permits more constant plasma concentrations and clinical effects than intermittent IV bolus dosing, without the pain associated with intramuscular injection. The most common approach in pediatric centers is to administer a low-dose basal opioid infusion, while permitting patients to use a patient-controlled analgesia (PCA) device to titrate the dosage above the infusion (see Chapter 61; Fig. 62-3). Compared with children given intermittent intramuscular morphine, children using PCA reported better pain scores. PCA has several other advantages: (1) dosing can be adjusted to account for individual pharmacokinetic and pharmacodynamic variation and for changing pain intensity during the day; (2) psychologically, the patient is more in control, actively coping with the pain; (3) overall opioid consumption is lower; (4) fewer side effects occur; and (5) patient satisfaction is generally much higher. Children as young as 5-6 yr can effectively use PCA. The device can be activated by parents or nurses—the latter practice known as PCA-by-proxy; PCA-by-proxy produces analgesia in a safe, effective manner for children who cannot activate the PCA demand button themselves because they are too young or intellectually or physically impaired. PCA overdoses occur when well-meaning, inadequately instructed parents pushed the PCA button in medically complicated situations with or without the use of PCA-by-proxy, highlighting the need for patient and family education, the use of protocols, and adequate nursing supervision.

**Local Anesthetics**

Local anesthetics are widely used in children for topical application, cutaneous infiltration, peripheral nerve block, epidural neuroaxial blocks, intrathecal infusions, and IV infusions (see Chapter 61; Table 62-8). Local anesthetics can be used with excellent safety and effectiveness. Local anesthetics interfere with neural transmission by blocking sodium channels. Excessive systemic dosing can cause seizures, central nervous system (CNS) depression, and by cardiac and arteriolar sodium channel blockade hypotension, arrhythmias, cardiac...
<table>
<thead>
<tr>
<th>DRUG</th>
<th>EQUIANALGESIC DOSES</th>
<th>PARENTERAL DOSING (WEIGHT)</th>
<th>IV: PO DOSE RATIO</th>
<th>ORAL DOSING (WEIGHT)</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IV</td>
<td>ORAL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;50 kg</td>
<td>&gt;50 kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 µg</td>
<td>100 µg</td>
<td>0.5-1 µg/kg q1-2h</td>
<td>Oral transmucosal: 1:10</td>
<td>Transdermal patches available; patch reaches steady state at 24 hr and should be changed q72h</td>
</tr>
<tr>
<td></td>
<td>0.5-1.5 µg/kg/hr</td>
<td></td>
<td></td>
<td></td>
<td>70-100 times as potent as morphine with rapid onset and shorter duration</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>N/A</td>
<td>1.5 mg</td>
<td>N/A</td>
<td>0.15 mg/kg</td>
<td>10 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Weak opioid; only available in form with acetaminophen</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.2 mg</td>
<td>0.6 mg</td>
<td>0.01 mg q2-4h</td>
<td>1:3</td>
<td>5x the potency of morphine; no histamine release and fewer adverse events than morphine</td>
</tr>
<tr>
<td></td>
<td>0.02 mg/kg/hr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meperidine</td>
<td>10 mg</td>
<td>30 mg</td>
<td>0.5 mg/kg q2-4h</td>
<td>1:4</td>
<td>100-150 mg q3-4h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Primary use in low doses is for treatment of rigors and shivering after anesthesia or with amphotericin or blood products Not appropriate for repeated dosing</td>
</tr>
<tr>
<td>Methadone</td>
<td>1 mg</td>
<td>2 mg</td>
<td>0.1 mg/kg q8-24h</td>
<td>1:2</td>
<td>2.5 mg tid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Duration 12-24 hr; useful in certain types of chronic pain; requires additional vigilance, because it will accumulate over 72 hr and produce delayed sedation When patients who are tolerant to opioids are switched to methadone, they show incomplete cross-tolerance and improved efficacy; because it is associated with prolonged QTc, monitoring is needed for children on high and extended dosing</td>
</tr>
<tr>
<td>Morphine</td>
<td>1 mg</td>
<td>3 mg</td>
<td>0.05 mg/kg q2-4h</td>
<td>1:3</td>
<td>15-20 mg q3-4h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Potent opioid for moderate/severe pain; may cause histamine release Sustained-release form must be swallowed whole; if crushed, becomes immediate-acting, leading to acute overdose</td>
</tr>
<tr>
<td></td>
<td>Bolus: 5-8 mg q2-4h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>N/A</td>
<td>3 mg</td>
<td>N/A</td>
<td>0.1-0.2 mg q3-4h; 10-120 mg q8-12h</td>
<td>Strong opioid only available as an oral agent in North America; more potent than and preferable to hydrocodone Sustained-release form must be swallowed whole; if crushed, becomes immediate-acting, leading to acute overdose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N/A, not available.
Management of Opioid-Induced Adverse Effects

<table>
<thead>
<tr>
<th>Table 62-6</th>
<th>Management of Opioid-Induced Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory depression</strong></td>
<td>Naloxone: 0.01-0.02 mg/kg up to a full reversal dose of 0.1 mg/kg. May be given IV, IM, subcutaneously (SC), or via endotracheal tube (ET). The full reversal dose should initially be used for apnea in opioid-naïve patients. In opioid-tolerant patients, a reduced dose should be given and titrated up slowly to treat symptoms but prevent acute withdrawal. Ventilation may need to be supported during this process. Dose may be repeated every 2 min to a total of 10 mg. Adult maximum dose is 2 mg/dose. Give with caution to patients who are receiving long-term opioid therapy, as it may precipitate acute withdrawal. Duration of effect is 1-4 hr; therefore, close observation for renarcotization is essential.</td>
</tr>
<tr>
<td><strong>Excessive sedation without evidence of respiratory depression</strong></td>
<td>Methylphenidate(^*): 0.3 mg/kg per dose PO (typically 10-20 mg/dose to a teenager) before breakfast and lunch. Do not administer to patients receiving clonidine, because dysrhythmias may develop. Dextroamphetamine: 2.5-10 mg on awakening and at noon. Not for use in young children or in patients with cardiovascular disease or hypertension. Modafinil: Pediatric dose not established. May be useful in selected patients. Typical adult dose: 50-200 mg/day. Change opioid or decrease dose.</td>
</tr>
<tr>
<td><strong>Nausea and vomiting</strong></td>
<td>Metoclopramide(^1): 0.15 mg/kg IV up to 10 mg/dose q6-12h for 24 hr. Trimethobenzamide: PO or rectally (PR) if weight &lt;15 kg, 100 mg q6h; if &gt;15 kg, 200 mg q6h. (Note: Suppository contains benzoic acid.) Not for use in newborn infants or premature infants. 5-HT(_3) blockers: Ondansetron: 0.15 mg/kg up to 8 mg IV q6-8h not to exceed 32 mg/day (also available as a sublingual tablet). Granisetron: 10-20 µg/kg IV q12-24h. Prochlorperazine(^\ast): (Compazine): &gt;2 yr or &gt;20 kg, 0.1 mg/kg per dose q6h IM or PO up to 10 mg/dose. Change opioid.</td>
</tr>
<tr>
<td><strong>Pruritus</strong></td>
<td>Hydroxyzine: 0.5 mg/kg PO q6h. Nalbuphine: 0.1 mg/kg IV q6h for pruritus caused by intraaxial opioids, especially fentanyl. Administer slowly over 15-20 min. May cause acute reversal of systemic (\mu)-receptor effects and leave (\kappa)-agonism intact. Naloxone: 0.003-0.1 mg/kg/hr IV infusion (titrate up to decrease pruritus and reduce infusion if pain increases). Ondansetron: 0.05-0.1 mg/kg IV or PO q8h. Cyproheptadine(^1): 0.1-0.2 mg/kg PO q8-12h. Maximum dose 12 mg. Change opioid.</td>
</tr>
<tr>
<td><strong>Constipation</strong></td>
<td>Encourage water consumption, high-fiber diet, and vegetable roughage. Bulk laxatives: Metamucil, Maltasupex. Lubricants: Mineral oil 15-30 mL PO qd as needed (not for use in infants because of aspiration risk). Surfactants: Sodium docusate (Colace): &lt;3 yr: 10 mg PO q8h 3-6 yr: 15 mg PO q8h 6-12 yr: 50 mg PO q8h &gt;12 yr: 100 mg PO q8h Stimulants: Bisacodyl suppository (Dulcolax): &lt;2 yr: 5 mg PR qhs &gt;2 yr: 10 mg PR qhs Senna syrup (218 mg/5 mL): &gt;3 yr, 5 mL qhs. Enema: Fleet’s hypertonic phosphate enema (older children; risk of hyperphosphatemia). Electrolytic/osmotic: Milk of magnesia; for severe impaction: polyethylene glycol (GoLYTELY, MiraLAX).</td>
</tr>
</tbody>
</table>

*Avoid in patients taking monoamine oxidase inhibitors.

1 May be associated with extrapyramidal side effects, which may be more commonly seen in children than in adults.


### Table 62-8 Classes of Local Anesthetic Drugs

<table>
<thead>
<tr>
<th>Amides are metabolized in the liver and the elimination half-lives vary from about 1.5-3.5 hr</th>
<th>Lidocaine (lignocaine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine</td>
<td>Prilocaine</td>
</tr>
<tr>
<td>Dibucaine (cinchocaine)</td>
<td>Mepivacaine</td>
</tr>
<tr>
<td>Eutradacaine</td>
<td>Ropivacaine</td>
</tr>
</tbody>
</table>

| Esters are metabolized in plasma (and to a lesser extent the liver) by pseudocholinesterases; thus their half-lives in the circulation are shorter than those of amides | Procaine |
| Chloroprocaine |
| Cocaine |
| Tetracaine (amethocaine) |
| Benzocaine |


### Table 62-9 Examples of Neuropathic Pain Syndromes

**PERIPHERAL NERVOUS SYSTEM FOCAL AND MULTIFOCAL LESIONS**
- Postherpetic neuralgia
- Cranial neuralgias (such as trigeminal neuralgia, glossopharyngeal neuralgia)
- Diabetic mononeuropathy
- Nerve entrapment syndromes
- Plexopathy from malignancy or irradiation
- Phantom limb pain
- Posttraumatic neuralgia (such as nerve root compression after thoracotomy)
- Ischemic neuropathy

**PERIPHERAL NERVOUS SYSTEM GENERALIZED POLYNEUROPATHIES**
- Metabolic/nutritional: Diabetes mellitus, pellagra, beriberi, multiple nutritional deficiency, hypothyroidism
- Toxic: Alcohol-, platinum-, or taxane-based chemotherapy, isoniazid, antiretroviral drugs
- Infective/autoimmune: HIV, acute inflammatory polyneuropathy (Guillain-Barré syndrome), neuroborreliosis (Bannwarth syndrome)
- Hereditary: Fabry disease
- Malignancy: Carcinomatosis
- Others: Idiopathic small fiber neuropathy

**CENTRAL NERVOUS SYSTEM LESIONS**
- Spinal cord injury
- Pseudosepse disc
- Stroke (brain infarction, spinal infarction)
- Multiple sclerosis
- Surgical lesions (such as rhizotomy, cordotomy)
- Complex neuropathic disorders
- Complex regional pain syndrome types I and II


### Table 62-7 Equianalgesic Doses and Half-Lives (T1/2) of Some Commonly Used Opioids

<table>
<thead>
<tr>
<th>OPIOID</th>
<th>IM/IV DOSE (mg)</th>
<th>ORAL DOSE (mg)</th>
<th>T1/2 (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10</td>
<td>30</td>
<td>2-3</td>
</tr>
<tr>
<td>Meperidine</td>
<td>100</td>
<td>400</td>
<td>3-4</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>15</td>
<td>20-30</td>
<td>2-3</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.15-0.2</td>
<td>—</td>
<td>3-5</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>0.75-1.5</td>
<td>—</td>
<td>1-2</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>0.02</td>
<td>—</td>
<td>2-3</td>
</tr>
<tr>
<td>Diamorphine</td>
<td>5</td>
<td>60</td>
<td>0.5*</td>
</tr>
<tr>
<td>Methadone</td>
<td>10</td>
<td>10-15</td>
<td>15-40</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5</td>
<td>7.5</td>
<td>3-4</td>
</tr>
<tr>
<td>Tramadol†</td>
<td>100</td>
<td>100</td>
<td>5-7</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>0.4</td>
<td>0.8 (sublingual)</td>
<td>3-5</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>60</td>
<td>150</td>
<td>3-5</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>10-20</td>
<td>—</td>
<td>2-4</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>2</td>
<td>—</td>
<td>2-3</td>
</tr>
</tbody>
</table>

**Notes:**
- Published reports vary in the suggested doses considered to be equianalgesic to morphine. Therefore, titration to clinical response in each patient is necessary.
- Suggested doses are the results of single-dose studies only. Therefore, use of the data to calculate total daily dose requirements and repeated or continuous doses may not be appropriate.
- There may be incomplete cross-tolerance between these drugs. In patients who have been receiving 1 opioid for a prolonged period, it is usually necessary to use a dose lower than the expected equianalgesic dose when changing to another opioid, and to titrate to effect.
- Rapidly hydrolyzed to morphine.
- Only part of its analgesic action results from action on β opioid receptors.


- depression, and cardiovascular collapse. Unlike opioids, local anesthetics therefore require a strict maximum dosing schedule. Pediatricians should be aware of the need to calculate these doses and adhere to guidelines.

- Topical local anesthetic preparations do not generally result in measurable systemic blood levels, and can reduce pain in diverse circumstances: suturing of lacerations, placement of peripheral IV catheters, lumbar punctures, and accessing of indwelling central venous ports. The application of tetracaine, epinephrine, and cocaine (TAC) results in good anesthesia for suturing wounds, but TAC should not be used on mucous membranes. Combinations of tetracaine with phenyleph-
Treatment Recommendations for Central Neuropathic Pain Adapted from Current Evidence-Based Literature

<table>
<thead>
<tr>
<th>MEDICATION CLASS/DRUG</th>
<th>RECOMMENDED STAGE OF TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTIDEPRESSANTS</strong></td>
<td></td>
</tr>
<tr>
<td>Tricyclics (amitriptyline, nortriptyline)</td>
<td>1st or 2nd</td>
</tr>
<tr>
<td>Serotonin and norepinephrine reuptake inhibitors (duloxetine, venlafaxine)</td>
<td>1st or 2nd</td>
</tr>
<tr>
<td><strong>ANTICONVULSANTS</strong></td>
<td></td>
</tr>
<tr>
<td>Pregabalin</td>
<td>1st or 2nd</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>1st or 2nd</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>2nd or 3rd (in pain after stroke)</td>
</tr>
<tr>
<td>Valproate</td>
<td>3rd</td>
</tr>
<tr>
<td>OPIOIDS*</td>
<td>2nd (in multiple sclerosis)</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>3rd</td>
</tr>
<tr>
<td><strong>MISCELLANEOUS</strong></td>
<td></td>
</tr>
<tr>
<td>Cannabinoids</td>
<td></td>
</tr>
<tr>
<td>Mexiletine</td>
<td></td>
</tr>
</tbody>
</table>

*MISCELLANEOUS* includes antiepileptic drugs (AEDs), and neurotropic drugs.

**UNCONVENTIONAL MEDICATIONS IN PEDIATRIC PAIN**

Unconventional analgesic medication refers to a wide number of drugs that were developed for other indications but that have been found to have analgesic properties. These drugs include some antidepressants, antiepileptic drugs (AEDs), and neurotropic drugs.

The unconventional analgesics are generally used to manage neuropathic pain conditions, migraine disorders, fibromyalgia syndrome, and some forms of functional chronic abdominal pain syndromes, but they are generally not used to manage surgical, somatic, or musculoskeletal pain. Figure 62-4 presents a decision-making tree that will help the physician select the appropriate analgesic category for various types of pain. The AED gabapentin confers analgesia as well as opioid-sparing benefits following major surgery in adults and in one well-conducted clinical trial in adolescents following spine surgery.

Although several unconventional analgesics have been approved by the FDA for analgesic uses, none has been specifically approved for use in youth with chronic pain. Thus, these drugs should be used with caution, with a focus on mitigating pain to allow a child to participate effectively in therapies and return to normal activity as soon as possible. The use of psychotropic medications should be guided by the principles applied to pharmacologic treatment of any symptom or disease. Target symptoms should be identified, and medication side effects monitored. To determine dosing regimens, the physician should consider the child’s weight and the effects that medical condition and other medications, such as psychotropic drugs, may have on the child’s metabolism. When available, therapeutic blood-level monitoring should be performed. Side effects should be addressed in detail with both parent and child, and specific instructions given for responding to possible adverse events. It may be necessary to directly address concerns about addiction, dependence, and tolerance in order to decrease treatment-related anxiety and improve medication adherence.

**Antidepressant Medications**

Antidepressant medications are useful in adults with chronic pain, including neuropathic pain, headaches, and rheumatoid arthritis, independent of their effects on depressive disorders. Antidepressants’ analgesic properties inhibit norepinephrine reuptake in the CNS. In children, because clinical trials have been limited, the practitioner should use antidepressants cautiously to treat chronic pain or associated depressive or anxiety symptoms. The FDA issued a “black box warning,” its strongest warning, to inform the public of a small but significant increase in suicidal thoughts and attempts in children and adolescents receiving antidepressants. A meta-analysis of studies involving children and adolescents receiving antidepressants indicated that no suicides had been completed. The pediatrician should address this issue with parents of patients being treated with antidepressants and should develop monitoring plans consistent with current FDA recommendations.

**Tricyclic Antidepressants**

Tricyclic antidepressants (TCAs), which have been studied most in children with chronic pain, are effective in pain relief for symptoms including neuropathic pain, functional abdominal pain, and migraine. The efficacy of TCAs may be based on inhibition of the neurochemical pathways involved in norepinephrine and serotonin reuptake and their interference with other neurochemicals involved in the perception or neural conduction of pain. Because sedation is the most common side effect of TCAs, these medications are also effective in treating the sleep disorders that frequently accompany pediatric pain. Biotransformation of TCAs is extensive in healthy children, so the child should be started on a bedtime dose, which may be able to then be titrated to a daily divided dose, with the larger dose given at bedtime. However, TCAs typically are administered only at bedtime. Pain symptoms usually remit at lower doses than those recommended or required for the treatment of mood disorders. Most children and adolescents do not require more than 0.25-0.5 mg/kg of amitriptyline or nortriptyline once a day at bedtime.

Attention should also be paid to hepatic microsomal enzyme metabolism, because CYP2D6 inhibitors, such as cimetidine and quinidine, can increase levels of TCAs. Anticholinergic side effects, which are remarkably uncommon in children in comparison with adults, often remit over time. Constipation, orthostatic hypotension, and...
Serotonin and Serotonin-Norepinephrine Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) have minimal efficacy in the treatment of a variety of pain syndromes in adults. SSRIs are very useful when symptoms of depression or anxiety disorders are present and cannot be addressed adequately by nonpharmacologic means. Although many SSRIs are used in practice with children, only fluoxetine has been approved by the FDA for use in children and adolescents. SSRIs have a significantly milder side-effect profile than do TCAs (most side effects of both are transient), and they have no anticholinergic side effects. Chief side effects include gastrointestinal symptoms, headaches, agitation, insomnia, sexual dysfunction, and anxiety. Rarely, hypotension, or the syndrome of inappropriate antidiuretic hormone secretion, may occur. Interactions with other medications that have serotonergic effects (trazodone, trazodone, tryptophan, and triptan migraine medication) may also occur. When these medications are used in combination, there is increased likelihood that a life-threatening serotoninergic syndrome may occur, with associated symptoms of myoclonus, hyperreflexia, autonomic instability, muscle rigidity, and delirium. There is also a discontinuation syndrome associated with shorter-acting SSRIs (paroxetine), which includes dizziness, lethargy, paresthesias, irritability, and vivid dreams. Dosages of medications should be tapered slowly over several weeks.

The selective serotonin-norepinephrine reuptake inhibitors duloxetine and venlafaxine demonstrate significant efficacy with chronic neuropathic and other pain syndromes because they inhibit both serotonin and norepinephrine reuptake, and they may directly block associated pain receptors as well. Venlafaxine has no pain indication labeling, but duloxetine is FDA approved for managing neuropathic pain (diabetic neuropathy) and fibromyalgia syndrome.

Because both SSRIs and selective serotonin-norepinephrine reuptake inhibitors have fewer anticholinergic side effects than TCAs, adherence to them is better than in psychiatric populations taking TCAs. Side effects of both types of drugs include gastrointestinal symptoms, hyperhidrosis, dizziness, and agitation, but these effects generally wane over time. Hypertension and orthostatic hypotension may occur; in addition, the patient’s blood pressure should be closely followed, and appropriate hydration should be stressed. Note that whereas appetite stimulation and weight gain are associated with all TCAs, duloxetine is often associated with weight loss, frequently a desirable side effect, especially in weight-conscious adolescent females.

Antiepileptic Drugs

Traditional anticonvulsants, such as carbamazepine and valproic acid, are believed to relieve chronic pain by blocking sodium (valproate and the gabapentinoids) or calcium channels (carbamazepine and oxcarbazepine) at the cellular neuronal level, thereby suppressing spontaneous electrical activity and restoring the normal threshold to depolarization of hypersensitive nociceptive neurons, without affecting normal nerve conduction. These medications are particularly useful in patients with mood disorders and neuropathic pain. In adults, the FDA has approved carbamazepine for trigeminal neuralgia and valproate for migraine prophylaxis, and pregabalin is approved in adults for neuropathic pain complicating diabetes, zoster, and for management of fibromyalgia. Anticonvulsant medications generally have gastrointestinal side effects in addition to sedation, anemia, ataxia, rash, and hepatitis toxicity. Carbamazepine and oxcarbazepine are associated with an increased incidence of Stevens-Johnson syndrome. Liver function values and a complete blood count should be obtained at start of therapy (baseline) and monitored with use of both these agents. These medications have narrow therapeutic windows and may have extreme variability in therapeutic blood medication levels, as well as multiple drug–drug interactions; also, they may produce liver disease and renal impairment. Drug levels should be measured with each dose increase and periodically thereafter. Carbamazepine, in particular, causes autoinduction of hepatic microsomal enzymes, which can further complicate obtaining a therapeutic medication level. Frequent pregnancy tests are useful in menstruating female adolescents taking valproate, because severe neural tube defects are associated with this medication.

Less-toxic AEDs have supplanted the use of valproate and carbamazepine in patients with pain. These agents have their own, sometimes troubling side effect profiles, but they are far less toxic than their predecessors and they do not require monitoring of liver function, bone marrow function, or therapeutic blood levels. They are also far less lethal in accidental or deliberate overdose.

Gabapentin, the most widely prescribed AED for the management of pain disorders, demonstrates efficacy in treating children with chronic pain, particularly neuropathic pain, and is playing an increasing role in the management of routine surgical pain. Gabapentin has proven effective in treating chronic headache disorders, and many neuropathic pain syndromes including complex regional pain syndromes, chemotherapy induced neuropathy, postherpetic neuralgia, and diabetic neuropathy in both children and adults. This agent has a relatively benign side-effect profile and few drug interactions. Side effects include somnolence, dizziness, and ataxia. Children occasionally demonstrate side effects not reported in adults—severe impulsive or oppositional behavior, agitation, and, occasionally, depression. These side effects do not seem to be dose related.

A molecularly similar AED, pregabalin, works by mechanisms similar to those of gabapentin but appears to have a better side-effect profile. Because it undergoes virtually no hepatic metabolism, pregabalin has no significant drug–drug interactions, a concern in patients with chronic pain, who frequently take multiple medications—for both the pain and the underlying medical condition associated with the pain.

Topiramate also demonstrates greater success than traditional anticonvulsants in treating trigeminal neuralgia in adults and in migraine prophylaxis. Topiramate therapy results more frequently in cognitive dysfunction and short-term memory loss compared with gabapentin or pregabalin, and these neurocognitive effects are particularly problematic for school-age children. The pediatrician should also be aware that in female adolescents, topiramate is associated with weight loss, whereas other anticonvulsants are typically associated with significant weight gain.

Benzodiazepines

Children and adolescents with chronic pain may have comorbid psychiatric conditions such as depressed mood, sleep disturbances, or anxiety disorders, including generalized anxiety disorder, separation anxiety, posttraumatic stress disorder, and panic attacks. Pervasive developmental disorders are also common in this population.
Psychologic factors can affect a youth's ability to cope with a pain disorder; a conditioned response to pain may be to feel out of control and to lead to increases in anxiety and pain. Conversely, the feeling of helplessness can sensitize the child to increasing amounts of pain, leading the child to perseverate on the pain, think catastrophically, and feel hopeless. Changes in children's normal routines, with a negative impact on participation in valued activities, may further promote hopelessness, resulting in increased pain experiences and development of a depressive disorder.

Benzodiazepines are anxiolytic medications that also have muscle relaxant effects. They are particularly appropriate in acute situations as valuable adjuncts to the management of pain in the hospital setting, because they inhibit painful muscle spasms in surgical patients, but more importantly because they suppress the anxiety that virtually every hospitalized child experiences, anxiety that interferes with restorative sleep and amplifies the child's perception of pain. Benzodiazepines are useful to calm children with anxiety and anticipatory anxiety about planned, painful procedures.

Because dependence, tolerance, and withdrawal may occur with prolonged use, benzodiazepines are generally not recommended for the routine management of chronic pain. In concert with psychotherapy, they help control anxiety symptoms that amplify the perception of pain. Infrequently, benzodiazepines may cause behavioral disinhibition, psychosis-like behaviors, or, in large doses, respiratory depression. When dosing these medications, the pediatrician should consider that many benzodiazepines are metabolized by the cytochrome P450 microsomal enzyme system. This issue may be less significant with lorazepam and oxazepam, which undergo 1st-pass hepatic conjugation. Side effects common to benzodiazepines include sedation, ataxia, anemia, increased bronchial secretions, and depressed mood. If a benzodiazepine is administered for more than several consecutive days, the dosage should be slowly tapered over 2 or more weeks; if therapy is abruptly discontinued, autonomic instability, delirium, seizures, and profound insomnia may occur. There are data that suggest that the use of benzodiazepines during hospitalization for serious disease, such as organ transplantation, might increase the risk of development of post-traumatic stress disorder.

**Antipsychotics and Major Sedatives**

Low doses of antipsychotic medications are often used to address more-severe anxiety and agitation sometimes associated with chronic pain. The use of these medications is controversial because the associated adverse events may be severe. Typical antipsychotics, including thioridazine (Mellaril), haloperidol (Haldol), and chlorpromazine (Thorazine), are associated with a decrease in seizure threshold, agranulocytosis, weight gain, cardiac conduction disturbances, tardive dyskinesia, orthostatic hypotension, hepatic dysfunction, and life-threatening laryngeal dystonia. These side effects are generally less severe with atypical antipsychotics. Because they may still occur, the pediatrician should obtain a baseline electrocardiogram, liver function tests, and complete blood count. If the pediatrician is using typical antipsychotics, an inventory of movement disturbances, such as the Abnormal Involuntary Movement Scale test, should be performed at baseline and at every follow-up visit, because movement disorders can worsen with abrupt withdrawal of medications or can become irreversible.

Atypical antipsychotics are generally associated with less-severe side-effect profiles, particularly with regard to side effects such as dyskinesias and dystonias. Use of olanzapine (Zyprexa), which is particularly helpful with insomnia and severe anxiety, requires assessing dyskinesias, orthostatic hypotension, hepatic dysfunction, and life-threatening agranulocytosis, which should generally be avoided as a treatment for children and adolescents with chronic pain. Aripiprazole (Abilify) has been used for severe anxiety and/or for treatment-resistant depression. All antipsychotics are associated with the rare, but potentially lethal neuroleptic malignant syndrome, which includes severe autonomic instability, muscular rigidity, hyperthermia, catatonia, and altered mental status.

**Nonpharmacologic Treatment of Pain**

Numerous psychologic and physical treatments for relieving pain, fear, and anxiety as well as enhancing functioning have been a mainstay of pediatric pain treatment and have excellent safety profiles and proven effectiveness. In the area of acute and procedural pain, nonpharmacologic strategies have long been used to help reduce distress in children undergoing medical procedures and surgery. Many of the behavioral methods aim to help children shift attention from pain and alter pain perception (e.g., distraction, hypnosis, imagery). In the treatment of chronic pain, cognitive-behavioral therapies (CBTs) are the most implemented nonpharmacologic treatment. CBT was developed with the goal of modifying social/environmental and behavioral factors that may exacerbate the child's experience of pain and pain-related disability. There are now several decades of research available on CBTs for pediatric chronic pain. Meta-analyses of randomized controlled trials of CBT interventions have found large positive effects of psychologic intervention on pain reduction in children with headache, abdominal pain, and fibromyalgia. Effective strategies include cognitive-behavioral skills training, parent training, relaxation therapy, and biofeedback. The relative or comparative effectiveness of different interventions has been examined in studies of headache and abdominal pain in children. Biofeedback and relaxation therapies have been found to have superior effects to pharmacologic treatments in reducing headache pain in children and adolescents. Similarly, for recurrent abdominal pain, positive effects for CBT were found relative to pharmaceutical, botanical, and dietary interventions (which had very weak evidence).

Nonpharmacologic treatments of pain may be generalized to other treatment needs. A child with cancer who learns self-hypnosis to reduce distress from lumbar punctures may successfully apply this skill to other stressful medical and nonmedical situations. When deciding how to incorporate nonpharmacologic techniques to treat pain, the practitioner should: (1) pay attention to the patient's environment, optimal positioning, and physical comfort; (2) seek to integrate nonpharmacologic techniques with appropriate analgesics; (3) give children (and family members) developmentally and situationally appropriate information as to what to expect, given the child's medical condition, procedures, and treatments; (4) include patients and their families in decision making to ensure an appropriate treatment choice and to optimize adherence to treatment protocols; and (5) above all, develop a communication plan among the different therapists, typically with the pediatrician as the case manager, so that the messages to the child and parent are consistent and the modes of therapy are organized into an integrative team approach.

**Cognitive-behavioral strategies** refer to techniques that teach children how to manage pain by learning new ways to think about the pain and to change behaviors associated with the pain. This includes strategies aimed at enhancing children's confidence and self-efficacy, decreasing fear of pain, and promoting exposure to previously avoided activities. In addition, pain coping skills may shift the child's attentional focus away from pain and painful stimuli. Behavioral strategies focused on modifying contingencies in the child's environment (such as parental responses to pain behaviors) may influence pain expression, leading to changes in how children behave or respond to pain. Strategies may also be aimed specifically at modifying individual and family coping (e.g., difficulties in social relationships, psychosocial distress).

**Parent and family education and/or psychotherapy**, particularly cognitive-behavioral family approaches, have been shown to be effective for treating chronic pain. Parents can learn to cope with their own distress and to understand pain mechanisms and appropriate treatment of pain. Key strategies include teaching parents to alter family patterns that may inadvertently exacerbate pain through developing behavior plans. Parents are taught to create plans for the child to manage the child's own symptoms and increase independent functioning. Often, all adult caregivers (e.g., parents and teachers) need
guidance on developing a behavioral incentive plan to help the child return to school, gradually increase attendance, and receive tutoring, after a prolonged, pain-related absence.

Other Psychologic or Psychiatric Treatment
In addition to pain, there may be other psychologic disorders (e.g., anxiety disorders, major depression) that should be identified and addressed either as part of or separate from the pain management plan. Individual psychotherapy or psychiatric intervention may be warranted to adequately treat a comorbid disorder. Relaxation techniques promote muscle relaxation and reduction of anxiety, which often accompanies and increases pain. Controlled breathing and progressive muscle relaxation are commonly used relaxation techniques for preschool-age and older children. Asking the child to focus on the breath and pretend to be blowing up a big balloon, while pursing the lips and exhaling slowly may help induce controlled breathing. Distraction helps a child of any age shift attention away from pain and onto other activities. Common attention sustainers in the environment include bubbles, music, video games, television, the telephone, conversation, school, and play. Asking children to tell stories, or asking parents to read to the child, and even mutual story-telling can be helpful distracters. Being involved with social, school, physical, or other activities helps the child in chronic pain to regain function. Hypnotherapy helps a child focus on an imaginative experience that is comforting, safe, fun, or intriguing. Hypnotherapy captures the child’s attention, alters his sensory experiences, reduces distress, reframes pain experiences, creates time distortions, helps the child dissociate from the pain, and enhances feelings of mastery and self-control. Children with chronic pain can use metaphor, for example, imagining they have overcome something feared because of pain in real life. As the child increases mastery of imagined experiences, the enhanced sense of control can be used during actual pain rehabilitation. Hypnotherapy is best for children of school age or older. Biofeedback involves controlled breathing, relaxation, or hypnotic techniques with a mechanical device that provides visual or auditory feedback to the child when the desired action is approximated. Common targets of actions include muscle tension, peripheral skin temperature through peripheral vasodilation, and anal control through rectal muscle contraction and relaxation. Biofeedback also enhances the child’s sense of mastery and control, especially for the child who needs more “proof” of change than that generated through hypnotherapy alone. Iyengar yoga was developed to achieve balance in mind, body, and spirit. This form of therapeutic yoga is especially effective for treating chronic pain; improving mood, energy, and sleep; and reducing anxiety. Iyengar yoga involves a series of asanas (body poses) oriented to the specific medical condition or symptoms. It uses props, such as blankets, bolsters, blocks, and belts, to support the body while the patient assumes more healing poses. Yoga promotes a sense of energy, relaxation, strength, balance, and flexibility and, over time, enhances a sense of mastery and control. In more advanced yoga, the child may learn certain types of breathing (pranayama) for added benefit. Mostly, through this form of yoga, the child learns mindfulness or being present and in the moment. By focusing on body and breath, the child can develop strategies to avoid ruminating about the past or worrying about the future.

Massage therapy involves the therapist’s touching and applying varied degrees of pressure on the child’s muscles. This massage is very useful for children with chronic pain and especially helpful for those with myofascial pain. There are several types of massage, including craniosacral therapy. For young children, it can be helpful to have parents learn and perform brief massage on their children before bedtime. Physical therapy can be especially useful for children with chronic, musculoskeletal pain, and for those deconditioned from inactivity. Exercise appears to specifically benefit muscle functioning, circulation, and posture, also improving body image, body mechanics, sleep, and mood. The physical therapist and the child can develop a graded exercise plan for enhancing the child’s overall function.

Acupuncture involves the placement of needles at specific acupuncture points along a meridian, or energy field, after a diagnosis of excess or deficient energy in that meridian as the primary cause of the pain is made by the acupuncturist. Acupuncture is a feasible, popular part of a pain management plan for children with chronic pain. Acupuncture alleviates chronic nausea, fatigue, and several chronic pain states, including migraine and chronic daily headaches, abdominal pain, and myofascial pain. Acupuncture also has efficacy in adults with myofascial pain, primary dysmenorrhea, sickle cell crisis pain, and sore throat pain. The acupuncturist must relate well to children so that the experience is not traumatic, because added stress would undo the benefits gained. Transcutaneous electrical nerve stimulation (TENS) is the use of a battery-operated tool worn on the body to send electrical impulses into the body at certain frequencies set by the machine. TENS is believed to be quite safe and can be tried for many forms of localized pain. Children often find TENS helpful and effective. Music and art therapy can be especially helpful for young and nonverbal children who would otherwise have trouble with traditional talk psychotherapies. Also, many creative children can more easily express fears and negative emotions through creative expression and, with the therapist’s help, learn about themselves in the process. Dance, movement, pet therapies, and aromatherapy have also been used and may be very helpful but have not been well studied in children for pain control.

Invasive Interventions in Treating Pain
Interventional neuraxial and peripheral nerve blocks provide intraoperative anesthesia, postoperative analgesia (see Chapter 61), treatment of acute pain (e.g., long bone fracture and the pain of acute pancreatitis), and contribute to the management of chronic pain (e.g., headaches, abdominal pain, complex regional pain syndromes [CRPS], and cancer pain). Even though interventional procedures are typically rarely used in nonmalignant chronic pain in children, they are described here so that the pediatrician will understand the different types of procedures that are more commonly carried out in adults and rarely described in pediatric texts. Regional anesthesia provides several benefits: (1) it is an alternative to or augmentation of opioid-based pain control, thereby minimizing the opioid side effects of nausea, vomiting, somnolence, respiratory depression, pruritus, constipation, and physical dependence; (2) it generally provides better quality pain relief because it interrupts nociceptive pathways and more profoundly inhibits endocrine stress responses; (3) it results in earlier ambulation in recovering surgical patients; (4) it helps prevent atelectasis in the setting of severe chest pain; and (5) it usually results in earlier discharge from the hospital. Theoretically, the interruption of nociceptive pathways in the periphery by regional anesthetics will prevent, or reverse the process of amplification of pain signals induced by nociception (CNS wind-up, glial cell activation, etc.). For postoperative pain, effective regional anesthesia and good analgesia reduce the risks of acute pain transitioning into chronic pain.

Regional anesthesia is considered safe and effective if performed by trained staff with the proper equipment. Most nerve blocks are performed by an anesthesiologist or pain management physician; a few are easily performed by a nonanesthesiologist with appropriate training.

Head and Neck Blocks
Primary pain syndromes of the head, such as trigeminal neuralgia, are distinctly unusual in the pediatric population, and few surgical procedures in the head and neck are amenable to regional anesthesia. Pain following tonsillectomy is not amenable to nerve blockade, and neuromuscular incisional pain is usually mitigated by local infiltration of local anesthetic into the wound margins by the surgeon. Headache disorders, very common in the pediatric age group, often respond well to block of the greater and lesser occipital nerves, which provide sensation to much of the cranial structures, from the anterior hairline to the cervical region. The greater occipital nerve can be blocked adjacent to the occipital artery, which can usually be identified at the occipital
ridge midway between the occipital prominence and the mastoid process by palpation, Doppler sound amplification, or visually by ultrasound. The lesser occipital nerves emerge from deeper layers midway between the greater occipital nerve and the mastoid process, where subcutaneous infiltration is effective.

**Upper-Extremity Blocks**

The brachial plexus block controls pain during surgical procedures or other lesions of the upper extremities. This block also protects the extremity from movement, reduces arterial spasm, and blocks sympathetic outflow to the upper extremity. The brachial plexus, responsible for cutaneous and motor innervation of the upper extremity, is an arrangement of nerve fibers originating from spinal nerves C5 through T1, extending from the neck into the axilla, arm, and hand. The brachial plexus innervates the entire upper limb, except for the trapezius muscle and an area of skin near the axilla. If pain is located proximal to the elbow, the brachial plexus may be blocked above the clavicle (roots and trunks); if the pain is located distal to the elbow, the brachial plexus may be blocked below it (cords and nerves). The block may be given as a single injection with a long-acting anesthetic (bupivacaine or ropivacaine, sometimes augmented with clonidine or dexmethasone to prolong block duration and intensity) to provide up to 12 hr of analgesia, or given via a catheter (to infuse local anesthetic) attached to a pump that can provide continuous analgesia over days or even weeks.

Anesthesiologists frequently use an IV regional block (or Bier block) with a local anesthetic in combination with a vasodilator such as phen tolamine and an NSAID (typically ketorolac) to manage the pain of CRPS. The technique requires placement of an IV cannula into the distal part of the affected extremity, exsanguination of the extremity by elevating and wrapping it in an elastic (Esmarch) bandage, and application of a double pneumatic tourniquet, which is then inflated. Local anesthetic with additives as indicated is then injected into the IV cannula, filling the exsanguinated vasculature. The tourniquet must remain inflated for at least 30 min to allow fixation of local anesthetic to tissues, which reduces peak blood concentration and toxicity upon tourniquet deflation. Although the anesthetic effect is limited to the time of tourniquet inflation, analgesia for pain disorders usually persists for days, weeks, or months after the block.

**Trunk and Abdominal Visceral Blocks**

Trunk blocks provide somatic and visceral analgesia and anesthesia for pain or surgery of the thorax and abdominal area. Sympathetic, motor, and sensory blockade may be obtained. These blocks are often used in combination to provide optimal relief. Intercostal and paravertebral blocks may be beneficial in those patients for whom an epidural injection or catheter is contraindicated, for example, in the patient with a coagulopathy. Respiratory function is maintained, and the side effects of opioid therapy are eliminated.

The intercostal, paravertebral, rectus sheath, and transverse abdominal plane blocks are the most useful ones for pediatric chest and abdominal pain. The celiac plexus block is most useful for visceral pain caused by malignant cancer or pancreatitis. A pediatrician may perform an intercostal block, but the other blocks are best performed by an experienced anesthesiologist or pain physician.

The intercostal block is used to block the intercostal nerves, the anterior rami of the thoracic nerves from T1 to T11. These nerve pairs lie inferior and posterior to each rib, and between the inner and innermost intercostal muscles, with their corresponding vein and artery, where they can be blocked, generally posterior to the posterior axillary line. Ultrasound imaging of the intercostal nerves helps avoid injury to intercostal vessels or insertion of the needle through the pleura, which results in pneumothorax.

The paravertebral block, an alternative to intercostal nerve block or epidural analgesia, is useful for pain associated with thoracotomy or with unilateral abdominal surgery, such as nephrectomy or splenectomy. Essentially this block results in multiple intercostal blocks with a single injection. The thoracic paravertebral space, lateral to the vertebral column, contains the sympathetic chain, rami communicantes, and dorsal and ventral roots of the spinal nerves. Because it is a continuous space, local anesthetic injection will provide sensory, motor, and sympathetic blockade to several dermatomes. The paravertebral block may be performed as a single injection, or, for a very prolonged effect, as a continuous infusion over several days or weeks via a catheter inserted in the paravertebral space. This block is best performed by an anesthesiologist or interventional pain physician.

Plexus blocks were once thought to be useful in the diagnosis and treatment of sympathetically mediated pain, CRPS, and other neuropathic pain conditions, but more recently large meta-analyses have shown their utility to be small. The peripheral sympathetic trunk is formed by the branches of the thoracic and lumbar spinal segments,
and it extends from the base of the skull to the coccyx. The sympathetic chain, which consists of separate ganglia containing nerves and autonomic fibers with separate plexuses, can be differentially blocked. These separate plexuses include the stellate ganglion in the lower neck and upper thorax, the celiac plexus in the abdomen, the second lumbar plexus for the lower extremities, and the ganglion impar for the pelvis. When blocks of these plexuses are performed, sympathectomy is obtained without attendant motor or sensory anesthesia.

The stellate ganglion block is indicated for pain in the face or upper extremity as well as for CRPS, phantom limb pain, amputation stump pain, or circulatory insufficiency of the upper extremities. The stellate ganglion arises from spinal nerves C7-T1 and lies anterior to the 1st rib. It contains ganglionic fibers to the head and upper extremities. Structures in close proximity include the subclavian and vertebral arteries anteriorly, the recurrent laryngeal nerve, and the phrenic nerve. The Chassaignac tubercle, the transverse process of the C6 vertebral body superior to the stellate ganglion, is a useful and easily palpable landmark for the block, but radiographic or ultrasound imaging is more typically used than surface anatomy and palpation.

The lumbar sympathetic block addresses pain in the lower extremity, CRPS, phantom limb pain, amputation stump pain, and pain from circulatory insufficiency. The lumbar sympathetic chain contains ganglionic fibers to the pelvis and lower extremities. It lies along the anterolateral surface of the lumbar vertebral bodies and is most often injected between the L2 and L4 vertebral bodies.

The analgesia produced by peripheral sympathetic blocks usually outlives the duration of the local anesthetic, often persisting for weeks or indefinitely. If analgesia is transient, the blocks may be performed with catheter insertion for continuous local anesthesia of the sympathetic chain over a period of days or weeks. Because precise radiographically guided placement of the needle and/or catheter is required for safety and success, sympathetic blocks are generally best performed by an anesthesiologist, interventional pain physician, or interventional radiologist.

**Epidural Anesthesia (Thoracic, Lumbar, and Caudal)**

Epidural anesthesia and analgesia are indicated for pain below the clavicles, management of CRPS, cancer pain unresponsive to systemic opioids, and pain limited by opioid side effects.

The 3 layers of the spinal meninges—the dura mater (outer), the arachnoid mater (middle), and the pia mater (inner)—envelop the spinal neural tissue. The subarachnoid space contains cerebrospinal fluid between the arachnoid mater and pia mater. The epidural space extends from the foramen magnum to the sacral hiatus. The epidural space, which contains fat, lymphatics, blood vessels, and the spinal nerves as they leave the spinal cord, separates the dura mater from the perivascular sheath surrounding vertebral bodies. In children, the fat in the epidural space is not as dense as in adults, predisposing to greater spread of the local anesthetic from the site of injection.

Epidural local anesthetics block both sensory and sympathetic fibers, and if the local anesthetic is of sufficient concentration, they also block motor fibers. Mild hypotension may occur, although it is unusual in children younger than 8 yr. Epidural local anesthetics high in the thoracic spine may also anesthetize the sympathetic nerves to the heart (the cardiac accelerator fibers), producing bradycardia. In addition to using local anesthetics, it is routine to use opioids and α-agonists in the epidural space. These agents have their primary site of action in the spinal cord, to which they diffuse from their epidural depot. Side effects of epidural opioid administration include delayed respiratory depression, particularly when hydrophilic opioids such as morphine are used. The risk of this effect requires that children receiving epidural opioids by intermittent injection or continuous infusion be monitored by continuous pulse oximetry and nursing observation, particularly during the 1st 24 hr of therapy or after significant dose escalations. Respiratory depression occurring after the 1st 24 hr of epidural opioid administration is distinctly unusual.

Epidural clonidine, an α2-agonist with μ-opioid analgesic properties, is associated with minimal risk and side effects. Although product labeling indicates use only in children with severe cancer pain, it is commonly used for routine postoperative pain as well as pain syndromes such as CRPS. Mild sedation is the most common side effect of epidural clonidine, and it is not associated with respiratory depression.

Because performing epidural blockade is technical and may result in spinal cord injury, it is best done by an anesthesiologist or pain physician skilled in the technique.

**INTRATECHAL ANALGESIA**

Intrathecal catheters infused with opioids, clonidine, ziconotide, and local anesthetics are occasionally applicable in pediatric patients suffering from intractable pain from cancer or other conditions. Typically, intrathecal catheters are attached to an implanted electronic pump containing a drug reservoir sufficient for several months of dosing. The technique is technical and best performed by an experienced pain management physician.

**NERVE ABLATION AND DESTRUCTION**

In infrequent pediatric cases, pain remains refractory in spite of maximal reliance upon oral and IV medications and nerve blockade. In these instances, temporary (ablation) or permanent (lytic) destruction of 1 or more nerves may be performed. These situations are rather extraordinary in children, and the techniques should be carefully weighed against the consideration of inducing permanent nerve destruction in a growing child with decades of life ahead. On the other hand, when pain is severe in life-limiting disease processes, the long-term considerations are less concerning, and these techniques should be discussed with a pain management specialist skilled in their performance.

**CONSIDERATIONS FOR SPECIAL PEDIATRIC POPULATIONS**

**Pain Perception and Effects of Pain on Newborns and Infants**

There are a number of sources of pain in the newborn period. These include acute pain (diagnostic and therapeutic procedures, minor surgery, monitoring), continuous pain (pain from thermal/chemical burns, postsurgical and inflammatory pain), and chronic or disease-related pain (repeated heelsticks, indwelling catheters, necrotizing enterocolitis, nerve injury, chronic conditions, thrombophlebitis). The most common sources of pain in healthy infants are acute procedures, such as heel lances, operations, and, in boys, circumcision.

In premature infants in the neonatal intensive care unit (NICU), there are many procedures performed. In the 1st wk of life, approximately 94% of preterm infants younger than 28 wk of gestational age are ventilated. Other procedures are heelsticks (the most commonly performed) and airway suctioning. Only a few of these procedures are preceded by any type of analgesia. Repeated handling and acute pain episodes sensitize the neonate to increased reactivity and stress responses to subsequent procedures they undergo as neonates or children. Typical stress responses include increases in heart rate, respiratory rate, blood pressure, and intracranial pressure. Cardiac vagal tone, transcutaneous oxygen saturation, carbon dioxide levels, and peripheral blood flow are decreased. Autonomic signs include changes in skin color, vomiting, gagging, hiccupping, diaphoresis, dilated pupils, and palmar and forehead sweating.

To assess pain in the newborn, it is critical to observe the infant for facial expression, body movements, crying, and any other atypical functional behaviors. The observer must consider the context in which the behavior is experienced. The infant’s state (agitated, alert, asleep) and gestational and post-gestational ages also affect behavioral stress responses.

Untreated pain in the newborn has serious short-term and longer-term consequences. There has been a shift in most NICUs to more liberal use of opioids. Nonetheless, morphine, the traditional gold standard of analgesia for acute pain, may not be very effective and may have adverse long-term consequences. No differences have been found in the incidence of severe intraventricular hemorrhage or in the mortality rate when infants receiving morphine are compared with the
placebo group, and there are no changes in assessed pain from tracheal suctioning in ventilated infants receiving morphine compared with those receiving a placebo infusion. Morphine may not alleviate acute pain in ventilated preterm neonates, although there are few data on the effects of morphine and fentanyl in nonventilated newborns. The lack of opioid effects for acute pain in neonates may be due to an immaturity of opioid receptors; acute pain may cause the uncoupling of μ opioid receptors in the forebrain. Repetitive acute pain may create central neural changes in the newborn that may have long-term consequences for later pain vulnerability, cognitive effects, and opioid tolerance. There are both anatomic and behavioral manifestations of the adverse effects of neonatal stress, including pain, on brain development. Most neonatologists use opioids in painful situations. Sucrose and pacifiers are also being used in the NICU. The effects of sucrose (sweet taste) are believed to be opioid-mediated because they are reversed with naloxone; stress and pain relief are integrated through the endogenous opioid system. Sucrose, with or without a pacifier, may be effective for acute pain and stress control. Other nonpharmacologic strategies for stress and pain control include infant care by an individual primary nurse, tactile-kinesthetic stimuli (massage), “kangaroo care,” and soothing sensorial saturation.

**Children with Cancer Pain**

The World Health Organization proposed an analgesic therapy model for cancer pain known as the *analgesic ladder* (Table 62-11). Designed to guide therapy in the Third World, this ladder consists of a hierarchy of oral pharmacologic interventions intended to treat pain increasing in magnitude. The hierarchy ignores modalities such as the use of nonconventional analgesics and interventional pain procedures, which are within the capability of physicians to prescribe in developed countries. Nevertheless, because oral medications are simple and efficacious, especially for home use, the ladder presents a framework for rationally using them before applying other drugs and techniques of drug administration.

Oral medications are the 1st line of analgesic treatment. Because NSAIDs affect platelet adherence, they are typically not used. Opioid therapy is the preferred approach for moderate or severe pain. Nonopioid analgesics are used for mild pain, a weak opioid is added for moderate pain, and strong opioids are administered for more severe pain. Adjuvant analgesics can be added, and side effects and comorbid symptoms are actively managed. Determining the type and sources of the pain will help develop an effective analgesic plan. Certain treatments, such as the chemotherapeutic agent vincristine, are associated with neuropathic pain. Such pain might require anticonvulsants or TCAs. Organ-stretching pain from tumor growth within an organ might require strong opioids and/or radiation therapy if the tumor is radiosensitive. Organ obstruction, such as intestinal obstruction, should be diagnosed to relieve or bypass the obstruction.

It is important to consider both pharmacologic and nonpharmacologic strategies (e.g., cognitive-behavioral treatment, family and parent support) to treat pain in children with cancer.

**Table 62-11**

<table>
<thead>
<tr>
<th>World Health Organization Analgesic Ladder for Cancer Pain</th>
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<tr>
<td><strong>STEP 1</strong> Patients who present with mild to moderate pain should be treated with a nonopioid.</td>
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<tr>
<td><strong>STEP 2</strong> Patients who present with moderate to severe pain or for whom the step 1 regimen fails should be treated with an oral opioid for moderate pain combined with a nonopioid analgesic.</td>
</tr>
<tr>
<td><strong>STEP 3</strong> Patients who present with very severe pain or for whom the step 2 regimen fails should be treated with an opioid used for severe pain, with or without a nonopioid analgesic.</td>
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</table>

**Children with Pain Associated with Advanced Disease**

Patients with advanced diseases, including cancer, AIDS, neurodegenerative disorders, and cystic fibrosis, need palliative care approaches that focus on optimal quality of life. Nonpharmacologic and pharmacologic means of management of pain and other distressing symptoms are palliative care’s key components. It should be highlighted here that “palliative care” should be offered to all children with serious diseases, whether or not the diseases are potentially curable and whether or not long life expectancy is predicted. Examples include young children diagnosed with acute lymphoblastic leukemia (>90% posttreatment life expectancy) and children undergoing organ transplantation. Palliative care in pediatrics is meant to connote treatment that focuses on symptom reduction, quality of life, and good family and clinical team communication. It is not just reserved for patients in hospice care or those at the end of life. Differences among these conditions that relate to the progression of underlying illness, associated distressing symptoms, and common emotional responses should shape individual treatment plans (see Chapter 43). For end-of-life care, more than 90% of children and adolescents with cancer can be made comfortable by standard escalation of opioids according to the World Health Organization protocol. A small subgroup (5%) has enormous opioid dose escalation to >100 times the standard morphine or other opiate infusion rate. In most of these cases, there is spread of solid tumors to the spinal cord, roots, or plexus, and signs of neuropathic pain are evident. Methadone given orally is often used in palliative care, not just end of life care, because of its long half-life and its targeting of both opioid and N-methyl-D-aspartate receptors. The type of pain experienced by the patient (neuropathic, myofacial) should determine the need for adjunctive agents. Complementary measures, such as massage, hypnotherapy, and/or spiritual care, should also be considered in palliative care. Although the oral route of opioid administration should be encouraged, especially to facilitate care at home if possible, some children are unable to take oral opioids. Transdermal and sublingual routes, as well as an intravenous infusion with a PCA, are likely next choices. Small, portable infusion pumps are convenient for home use. If venous access is limited, a useful alternative is to administer opioids (especially morphine or hydromorphone, but not methadone or meperidine) through continuous subcutaneous infusion, with or without a bolus option. A small (e.g., 22-gauge) cannula is placed under the skin and secured on the thorax, abdomen, or thigh. Sites may be changed every 3–7 days, as needed. As noted, alternative routes for opioids include the transdermal and oral transmucosal routes. These latter routes are preferred over IV and subcutaneous drug delivery when the patient is being treated at home.

**Examples of Chronic and Recurrent Pain Syndromes**

Chronic pain is defined as recurrent or persistent pain lasting longer than the normal tissue healing time, approximately 3–6 mo. Children may experience pain related to injury (e.g., burns) or a chronic or underlying disease process (e.g., cancer, arthritis); pain can also be the chronic condition itself (e.g., CRPS, fibromyalgia, functional abdominal pain). During childhood, abdominal, musculoskeletal, and headache pain are the most frequently occurring conditions. However, definitions of chronic pain do not take into account standard criteria for assessing particular pain symptoms or for evaluating the intensity or impact of pain, and therefore include individuals with varying symptoms and experiences. Consequently, in epidemiologic surveys, prevalence estimates vary widely. Overall prevalence rates for different childhood pains range from 4–88%. For example, an average of 13.5–31.8% of adolescents in a community sample reported having weekly abdominal, headache, or musculoskeletal pains. Most epidemiologic studies report prevalence and do not report the severity or impact of the pain. Research indicates that only a subset of children and adolescents with chronic pain (approximately 5%) experience moderate-severe disability, and this likely better represents the estimated population for whom help is needed to treat pain and associated problems.
COMPLEX REGIONAL PAIN SYNDROMES

Neuropathic pain is caused by abnormal excitability in the peripheral or CNS that may persist after an injury heals or inflammation subsides. The pain, which can be acute or chronic, is described as burning or stabbing and may be associated with cutaneous hypersensitivity (allodynia), distortion of sensation (dysesthesia), and amplification of nocuous sensations (hyperalgesia and hyperpathia). Neuropathic pain conditions may be responsible for >35% of referrals to chronic pain clinics, conditions that commonly include posttraumatic and posturgical peripheral nerve injuries, phantom pain after amputation, pain after spinal cord injury, and pain caused by metabolic neuropathies. Neuropathic pain typically responds poorly to opioids. In adults, evidence suggests the efficacy of TCAs (nortriptyline, amitriptyline) and anticonvulsants (gabapentin, pregabalin) for treatment of neuropathic pain (see Tables 62-9 and 62-10).

CRPS type 1, formerly known as reflex sympathetic dystrophy, is well-described in the pediatric population. CRPS type 1 is a syndrome of neuropathic pain that typically follows an antecedent and usually minor injury to an extremity without identifiable nerve injury. The syndrome of CRPS type 1 includes severe spontaneous neuropathic pain, hyperpathia, hyperalgesia, severe cutaneous allodynia to touch and cold, changes in blood flow (typically extremity cyanosis), and sweating. In more advanced cases, symptoms include dystrophic changes of the hair, nails, and skin, immobility of the extremity (dystonia), and muscle atrophy. In the most advanced cases, symptoms include ankylosis of the joints of the extremity. Specific causal factors in CRPS type 1 in both children and adults remain elusive, although coincidental events may be noted. CRPS type 2, formerly referred to as causalgia, is less common.

The syndromes of CRPS type 2 and CRPS type 1 are virtually identical, except that the former is associated with a well-defined peripheral nerve injury. Treatment of CRPS in children has been extrapolated from that in adults, with some low-level evidence for efficacy of physical therapy, cognitive-behavioral therapy, nerve blocks, TCAs, gabapentin, and some other related drugs. All experts in pediatric pain management agree on the value of aggressive physical therapy. Some centers provide aggressive therapy without the use of pharmacologic agents or Interventional nerve blocks; unfortunately, recurrent episodes may be seen in up to 50% of patients. Physical therapy can be extraordinarily painful for children to endure; it is tolerated only by the most stoic and motivated patients. If children have difficulty enduring the pain, there is a well-established role for using pharmacologic agents with or without peripheral or central neuraxial nerve blocks to render the affected limb sufficiently analgesic so that physical therapy can be tolerated. Pharmacologic interventions include the use of AEDs such as gabapentin and/or TCAs such as amitriptyline (see Fig. 62-4). Although there is clear evidence of a peripheral inflammatory component of CRPS, with release of cytokines and other inflammatory mediators from the peripheral nervous system in the affected limb, the use of antiinflammatory agents has been disappointing.

Commonly used nerve block techniques include sympathetic nerve blocks, IV regional anesthetics, epidural analgesia, and peripheral nerve blocks. In extreme and refractory cases, more invasive strategies have been reported, including surgical sympathectomy and spinal cord stimulation. Although an array of treatments have some benefit, the mainstay of treatment remains physical therapy emphasizing desensitization, strengthening, and functional improvement. Additionally, pharmacologic agents and psychologic and complementary therapies are important components of a treatment plan. Invasive techniques, although not curative, are valuable if they permit the performance of frequent and aggressive physical therapy that cannot be carried out otherwise. Some children with CRPS become so easily sensitized that persistent and bothersome pain may develop at the site of the invasive procedure. A good biopsychosocial evaluation will help determine the orientation of the treatment components. At this time, there are insufficient data to indicate the superior value of Interventional blocks, such as epidural anesthesia delivery, in children with CRPS type 1, over physical and psychologic interventions, with or without pharmacologic support.

MYOFASCIAL PAIN DISORDERS AND FIBROMYALGIA

Myofascial pain disorders are associated with tender points in the affected muscles as well as with muscle spasms (tight muscles). Treatment is targeted at relaxing the affected muscles through physical therapy, yoga, massage, and/or acupuncture. Rarely are pharmacologic muscle relaxants helpful other than for creating tiredness at night for sleep. Dry needling or injections of local anesthetic into the tender points has been advocated, but the data do not support this as a standard treatment. Similarly, although botulinum toxin injections may be used, no data support this practice in children. Often poor body postures, repetitive use of a part of the body not used to that movement, or carrying heavy backpacks initiates pain. When it becomes widespread with multiple tender points, the diagnosis may be made of juvenile fibromyalgia, which may or may not continue to subsequently become adult fibromyalgia. Likely there are different subtypes of widespread pain syndromes, and physical therapy is a key component of treatment. Psychologic interventions may play an important role to assist the child in resuming normal activities and to manage any psychologic comorbidities. Any pain rehabilitation plan should enhance return to full function. Because there is a high incidence of chronic pain in parents of children presenting with a chronic pain condition, especially fibromyalgia, attention to parent and family factors is important. Parent training may entail teaching the parent to model more appropriate pain coping behaviors and to recognize the child’s independent attempts to manage pain and function adaptively. Parents may also need referrals to obtain appropriate pain management for their own pain condition.

The drugs pregabalin and duloxetine have both been approved for management of fibromyalgia in adults in the United States, but there are no clinical studies confirming their effectiveness in children and adolescents.

ERYTHROMELALGIA

Erythromelalgia in children is generally primary, whereas in adults it may be either primary or secondary to malignancy or other hematologic disorders such as polycythemia vera. Patients with this disorder exhibit red, warm, hyperperfused distal limbs. The disorder is usually bilateral, and it may involve either or both the hands and feet. Patients perceive burning pain and typically seek relief by immersing the affected extremities in ice water, sometimes so often and for so long so that skin pathology results. Primary erythromelalgia has recently been shown to be caused by a genetic mutation in the gene for the NaV1.7 neuronal sodium channel on peripheral C nociceptive fibers, resulting in their spontaneous depolarization, and thus continuous burning pain. The most common mutation identified is in the SCN9A gene, although there are several mutations that affect the NaV1.7 channel. Interestingly, another mutation in the NaV1.7 channel results in a rare but devastating genetic condition, the congenital indifference to pain.

It is easy to distinguish erythromelalgia (or related syndromes) from CRPS. The limb afflicted with CRPS is typically cold and cyanotic, the disease is typically unilateral, and children with CRPS have cold alloodynia, making immersion in cold water exquisitely painful; in erythromelalgia, ice water immersion is analgesic, the condition is bilateral and symmetrical, and associated with hyperperfusion of the distal extremity. The evaluation of hyperperfused limbs with burning pain should include genetic testing for Fabry disease and screening for hematologic malignancies, with diagnosis of primary erythromelalgia being one of exclusion. There are presently few clinical laboratories that are certified to perform the DNA analysis required to identify the common NaV1.7 mutations.

The definitive treatment of Fabry disease includes enzyme replacement as disease-modifying treatment and administration of neurophathic pain medications, such as gabapentin, although the success of antineuropathic pain drugs in small-fiber neuropathies has not been impressive. The treatment of erythromelalgia is far more problematic. Antineuropathic pain medications, such as AEDs and TCAs are typically prescribed but rarely helpful (see Fig. 62-4). Although one might predict that sodium channel–blocking AEDs might be effective in this
sodium channelopathy, oxcarbazepine has not proven to be a particularly effective modality. The pain responds well to regional anesthetic nerve blocks, but it returns immediately when the effects of the nerve block resolve. In contrast, in other neuropathic syndromes, the analgesia usually (and inexplicably) persists well after the resolution of the pharmacologic nerve block. Aspirin and even nitroprusside infusions are reported to be of benefit with secondary erythromelalgia, but they are not reported to be helpful in children with primary erythromelalgia. There are case reports in adults and clinical experience in children suggesting that periodic treatment with high-dose capsaicin cream is effective in alleviating the burning pain and disability of erythromelalgia. Capsaicin (essence of chili pepper) cream is a vanilloid receptor (TRPV1) agonist that depletes small-fiber peripheral nerve endings of the neurotransmitter substance P, which is an important neurotransmitter in the generation and transmission of nociceptive impulses. Once depleted, these nerve endings are no longer capable of generating spontaneous pain until the receptors regenerate, a process that takes many months.

OTHER CHRONIC PAIN CONDITIONS IN CHILDREN

It should be noted that there are a variety of genetic and other medical/surgical conditions that are often associated with chronic pain. Examples include Fabry disease, Chiari/syringomyelia, juvenile idiopathic arthritis, mitochondrial disorders, degenerative neurologic diseases, cerebral palsy, autism spectrum disorders, intestinal pseudoobstruction, inflammatory bowel disease, chronic migraine and chronic daily headaches, irritable bowel disease, and others. In many cases, treating the underlying disease, such as enzyme replacement in Fabry disease and in other lysosomal disorders, will reduce what otherwise might be progression of symptoms, but may not totally reduce pain and suffering, and other modalities will be needed. Finally, pain that persists and is not well treated can lead to central sensitization and widespread pain, such as seen in children with one pain source who develop fibromyalgia.

MANAGING COMPLEX CHRONIC PAIN PROBLEMS

Some patients with chronic pain have a prolonged course of evaluation in attempts to find what is expected as the singular “cause” of the pain, and thus also undergo many failed treatments. Parents worry that the doctors have not yet discovered the cause that may be serious and life-threatening, and children often feel not believed, that they are faking their pain, or are “crazy.” There may be no identifiable or diagnosable condition and families may seek opinions from multiple treatment facilities in an attempt to find help for their suffering child. In fact, in many cases, what may have begun as an acute injury or infectious event may result for some children into a chronic pain syndrome, with changes in the neurobiology of the pain signaling system.

In the context of disabling chronic pain, it is very important for the pediatrician to (1) avoid overmedication because this can exacerbate associated disability, (2) maintain an open mind and reassess the diagnosis if the clinical presentation changes, and (3) understand and communicate to the family that pain has a biologic basis (likely related to neural signaling and neurotransmitter dysregulation), and the pain is naturally distressing to the child and family. All patients and families should receive a simple explanation of pain physiology that helps them understand the importance of (1) functional rehabilitation to normalize pain signaling, (2) the low risk of causing further injury with systematic increases in normal functioning, and (3) the likely failure of treatment if pain is managed as if it were acute. Because it is counter-intuitive for most people to move a part of the body that hurts, many patients with chronic pain have atrophy or contractures of a painful extremity from disuse. Additionally, associated increases in worry and anxiety may exacerbate pain and leave the body even more vulnerable to further illness, injury, and disability. Pain can have a significant impact on many areas of normal functioning and routine for children, and school absenteeism and related consequences of missed schooling are often significant problems. Appropriate assessment and evaluation of the child with chronic pain and the child’s family is the critical first step necessary in developing a treatment plan.

Interdisciplinary pediatric pain programs have become the standard of care for treating complex chronic pain problems in youth. In recognition of the severity and complexity of pain and disability for some children, different settings and treatment delivery models for providing pain care have been explored. One option is inpatient and day hospital treatment programs. They often address barriers to access to outpatient treatment and coordination of care. In addition, they provide an intensive treatment option for children who do not make adequate progress in outpatient treatment or who are severely disabled by pain. Early programs developed in the 1990s focused on treatment of CRPS through intensive inpatient rehabilitation and exercise-based treatment programs. Later developing programs expanded to other clinical populations and expanded the treatment focus to incorporate a range of rehabilitation and psychologic therapies delivered both individually and in groups. The typical length of inpatient admissions for children with chronic pain in such programs is 3-4 wk and there is emerging evidence to suggest benefit from these programs.

Another intervention delivery option is remote management, referring to pain interventions utilized outside of the clinic/hospital setting to reach children in their homes or communities. Interventions are typically delivered using some form of technology, such as the Internet, or rely on other media such as telephone counseling or use of written self-help materials. Most typically, remote management of pain includes monitoring, counseling, and/or delivery of behavioral and CBT interventions. Internet interventions have received the most research attention to date with published examples for several different pediatric chronic pain conditions with promising findings for pain reduction. Telemedicine, while in widespread use clinically for many pediatric health conditions, has not yet been formally evaluated in pediatric pain. Within any community, the pediatrician will need to locate appropriate referral sources for patients with complex chronic pain.

Bibliography is available at Expert Consult.
Poisoning is now the number 1 cause of injury death in the United States, even surpassing that from motor vehicle collisions. The majority of these deaths are unintentional (i.e., not suicide). In adolescents, poisoning is the third leading cause of injury-related death. Of the more than 2 million human poisoning exposures reported annually to the National Poison Data Systems of the American Association of Poison Control Centers, approximately 50% occur in children younger than 6 yr old. Almost all of these exposures are unintentional and reflect the propensity for young children to put virtually anything in their mouths. Fortunately, children younger than 6 yr account for <2% of all poisoning fatalities reported to National Poison Data Systems.

More than 90% of toxic exposures in children occur in the home, and most involve only a single substance. Ingestion accounts for the vast majority of exposures, with a minority occurring via the dermal, inhalational, and ophthalmic routes. Approximately 50% of cases involve nondrug substances, such as cosmetics, personal care items, cleaning solutions, plants, and foreign bodies. Pharmaceutical preparations account for the remainder of exposures, and analgesics, topical preparations, cough and cold products, and vitamins are the most commonly reported categories.

The majority of poisoning exposures in children younger than 6 yr can be managed without direct medical intervention (beyond a call to
Part VIII  Pediatric Drug Therapy

Table 63-1  Common Agents Potentially Toxic to Young Children (<6 yr) in Small Doses

<table>
<thead>
<tr>
<th>SUBSTANCE</th>
<th>TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aliphatic hydrocarbons (e.g.,</td>
<td>Acute lung injury</td>
</tr>
<tr>
<td>gasoline, kerosene, lamp oil)</td>
<td></td>
</tr>
<tr>
<td>Antimalarials (chloroquine, quinine)</td>
<td>Seizures, dysrhythmias</td>
</tr>
<tr>
<td>Benzocaine</td>
<td>Methemoglobinemia</td>
</tr>
<tr>
<td>β Blockers (lipid-soluble β</td>
<td>Bradycardia, hypotension</td>
</tr>
<tr>
<td>blockers [e.g., propranolol]</td>
<td></td>
</tr>
<tr>
<td>are more toxic than water-soluble</td>
<td></td>
</tr>
<tr>
<td>β blockers [e.g., atenolol])</td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Bradycardia, hypotension, hyperglycemia</td>
</tr>
<tr>
<td>Camphor</td>
<td>Seizures</td>
</tr>
<tr>
<td>Caustics (pH &lt;2 or &gt;12)</td>
<td>Airway, esophageal and gastric burns</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Lethargy, bradycardia, hypotension</td>
</tr>
<tr>
<td>Diphenoxylate and atropine (Lomotil)</td>
<td>CNS depression, respiratory depression</td>
</tr>
<tr>
<td>Hypoglycemics, oral (sulfonyleurans</td>
<td>Hypoglycemia, seizures</td>
</tr>
<tr>
<td>and meglitinides)</td>
<td></td>
</tr>
<tr>
<td>Laundry detergent packets (pods)</td>
<td>Airway issues, respiratory distress, altered</td>
</tr>
<tr>
<td></td>
<td>mental status</td>
</tr>
<tr>
<td>Lindane</td>
<td>Seizures</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors</td>
<td>Hypertension followed by delayed cardiovascular collapse</td>
</tr>
<tr>
<td>Methyl salicylate</td>
<td>Tachypnea, metabolic acidosis, seizures</td>
</tr>
<tr>
<td>Opioids (especially methadone</td>
<td>CNS depression, respiratory depression</td>
</tr>
<tr>
<td>(buprenorphine)</td>
<td></td>
</tr>
<tr>
<td>Organophosphate pesticides</td>
<td>Cholinergic crisis</td>
</tr>
<tr>
<td>Phenothiazines (especially</td>
<td>Seizures, dysrhythmias</td>
</tr>
<tr>
<td>chlorpromazine, thiophiadazine)</td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td>Seizures, dysrhythmias</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>CNS depression, seizures, dysrhythmias,</td>
</tr>
<tr>
<td></td>
<td>hypotension</td>
</tr>
</tbody>
</table>

*Small dose* typically implies 1 or 2 pills or 5 mL. CNS, central nervous system.

the regional poison control center), either because the product involved is not inherently toxic or the quantity of the material involved is not sufficient to produce clinically relevant toxic effects. However, a number of substances are potentially highly toxic to toddlers in small doses (Table 63-1). In 2012, carbon monoxide and analgesics (acetaminophen and salicylate) were the leading causes of poisoning fatalities in young children (<6 yr). In addition, prescription opioids, antidepressants, cardiovascular drugs, and aliphatic hydrocarbons were significant causes of mortality.

Poison prevention education should be an integral part of all well-child visits, starting at the 6 mo visit. Counseling parents and other caregivers about potential poisoning risks, how to poison-proof a child's environment, and what to do if an ingestion or exposure occurs diminishes the likelihood of serious morbidity or mortality. Poison prevention education materials are available from the American Academy of Pediatrics and regional poison control centers. A network of poison control centers exists in the United States, and anyone at any time can contact a regional poison center by calling this toll-free number: 1-800-222-1222. Parents should be encouraged to share this number with grandparents, relatives, babysitters, and any other caregivers.

Product safety measures, poison prevention education, early recognition of exposures, and around-the-clock access to regionally based poison control centers all contribute to the favorable outcomes in young children. Poisoning exposures in children 6-12 yr old are much less common, involving only approximately 6% of all reported pediatric exposures. A second peak in pediatric exposures occurs in adolescence. Exposures in the adolescent age group are primarily intentional (suicide or abuse or misuse of substances) and thus often result in more severe toxicity (see Chapter 114). Families should be informed and given anticipatory guidance that nonprescription and prescription medications, and even household products (e.g., inhalants), are common sources of adolescent exposures. Adolescents (ages 13-19 yr) accounted for 45 of the 73 poison-related pediatric deaths in 2012 reported to National Poison Data System (4% of all fatalities called in to poison centers). Pediatricians should be aware of the signs of drug abuse or suicidal ideation in this population and should aggressively intervene (see Chapter 114).

**PREVENTION**

Deaths caused by unintentional poisoning among younger children have decreased dramatically over the past 2 decades, particularly among children younger than 5 yr of age. In 1970, when the Poison Packaging Prevention Act was passed, 226 poisoning deaths of children younger than 5 yr occurred compared with only 21 in 2012. Poisoning prevention demonstrates the effectiveness of passive strategies, including the use of child-resistant packaging and limited doses per container. Difficulty using child-resistant containers by adults is an important cause of poisoning in young children today; in 18.5% of households in which poisoning occurred in children younger than 5 yr of age, the child-resistant closure was replaced, and 65% of the packaging used did not work properly. Nearly 20% of ingestions occur from drugs owned by grandparents, a group that has difficulty using traditional child-resistant containers.

Even though there has been success in preventing poisoning in young children, there has been a remarkable rise in poison-related death over the past 20 yr in the adolescent population. This has mirrored the ever-increasing rate of opioid prescriptions written by healthcare providers.

**APPROACH TO THE POISONED PATIENT**

The initial approach to the patient with a witnessed or suspected poisoning should be no different than that in any other sick child, starting with stabilization and rapid assessment of the airway, breathing, circulation, and mental status (see Chapter 67). In any patient with altered mental status, a serum dextrose concentration should be obtained early and naloxone administration should be considered. A targeted history and physical examination serves as the foundation for a thoughtful differential diagnosis, which can then be further refined through laboratory testing and other diagnostic studies.

**INITIAL EVALUATION**

**History**

Obtaining an accurate problem-oriented history is of paramount importance. Intentional poisonings (suicide attempts; abuse or misuse) are typically more severe than unintentional, exploratory ingestions. In patients without a witnessed exposure, historical features such as age of the child (toddler or adolescent), acute onset of symptoms without prodrome, sudden alteration of mental status, multiple system organ dysfunction, or high levels of household stress should suggest a possible diagnosis of poisoning.

**Description of the Exposure**

For household and workplace products, names (brand, generic, chemical) and specific ingredients, along with their concentrations, can often...
be obtained from the labels. Poison control center specialists can also help to identify possible ingredients and review the potential toxicities of each component. In cases of suspected ingestion, poison center specialists can help identify pills based on markings, shape, and color. If referred to the hospital for evaluation, parents should be instructed to bring the products, pills, and/or containers with them to assist with identifying and quantifying the exposure. If a child is found with an unknown pill in the child’s mouth, the history must include a list of all medications in the child’s environment (including medications that grandparents, parents, siblings, caregivers, or other visitors might have brought into the house). In the case of an unknown exposure, clarifying where the child was found (e.g., garage, kitchen, laundry room, bathroom, backyard, workplace) can help to generate a list of potential toxins.

Next, it is important to clarify the timing of the ingestion and to obtain some estimate of how much of the substance was ingested. It is better to overestimate the amount ingested to prepare for the worst-case scenario. Counting pills or measuring the remaining volume of a liquid ingested can sometimes be useful in generating estimates. For inhalational, ocular, or dermal exposures, the concentration of the agent and the length of contact time with the material should be determined if possible.

Symptoms
Obtaining a description of symptoms experienced after ingestion, including their timing of onset relative to the time of ingestion and their progression, can generate a list of potential toxins and to predict the severity of the ingestion. Coupled with physical exam findings, reported symptoms assist practitioners in identifying toxidromes or recognized poisoning syndromes suggestive of poisoning from specific substances or classes of substances (Tables 63-2, 63-3, and 63-4).

Past Medical History
Underlying diseases can make a child more susceptible to the effects of a toxin. Concurrent drug therapy can also increase susceptibility because certain drugs may interact with the toxin. Pregnancy is a common precipitating factor in adolescents’ suicide attempts and can influence both evaluation of the patient and subsequent treatment. A history of psychiatric illness can make patients more prone to substance abuse, misuse, intentional ingestions, and polypharmacy complications. A developmental history is important to ensure that the history provided is appropriate for the child’s developmental stage (e.g., a report of a 6 mo old picking up a large container of laundry detergent and drinking it should raise a red flag).

Social History
Understanding the child’s social environment helps to identify potential sources of exposures (caregivers, visitors, grandparents, recent parties or social gatherings) and environmental stressors (new baby, parent’s illness, financial stress) that might have contributed to the ingestion. Unfortunately, some poisonings occur in the setting of serious neglect or intentional abuse.

Physical Examination
A targeted physical exam is important to identifying the potential toxin and assessing the severity of the exposure. Initial efforts should be directed toward assessing and stabilizing the airway, breathing, circulation, and mental status. Once one has ensured that the airway is secure and the patient is stable from a cardiopulmonary standpoint, a more extensive physical exam can help to identify characteristics of specific toxins or classes of toxins.

In the poisoned patient, the key features of the physical exam are the vital signs, mental status, pupils (size, reactivity) nystagmus, skin, bowel sounds, and odors. These findings might suggest a toxidrome that can guide the differential diagnosis and initial management.

Laboratory Evaluation
For select intoxications (e.g., salicylates, some anticonvulsants, acetaminophen, iron, digoxin, methanol, lithium, ethylene glycol, carbon monoxide, lead), quantitative blood concentrations are integral to confirming the diagnosis and formulating a treatment plan. For most exposures, quantitative measurement is not readily available and is not likely to alter management. All intoxicant levels must be interpreted in conjunction with the history. For instance, a methanol level of 20 mg/dL 1 hr after ingestion may well be nontoxic, whereas a similar level 24 hr after ingestion implies a patient with significant poisoning. In general, patients with multiple or chronic exposures to a drug or other chemical will be more symptomatic at lower drug levels than those with a single exposure.

Both urine drug-of-abuse screens and the more comprehensive drug screens vary widely in their ability to detect toxins and generally add little information to the clinical assessment, particularly if the agent is known and the patient’s symptoms are consistent with that agent. If a drug screen is ordered, it is important to know that the components screened for, and the lower limits of detection, vary from laboratory to laboratory. In addition, the interpretation of most drug screens is hampered by false-positive and false-negative results; standard urine opiate screens will not be positive after exposure to a synthetic opioid (e.g., methadone, buprenorphine, fentanyl). The urine drug-of-abuse screen is typically of limited utility when it comes to medical clearance, but does serve a useful function for psychiatrists in their evaluation of the adolescent patient. Apart from its psychiatric usefulness, urine drug-of-abuse screens are potentially helpful in patients with altered mental status of unknown etiology, persistent, unexplained tachycardia, acute myocardial ischemia or stroke at a young age, and in the assessment of a neglected or abused child. Consultation with a medical toxicologist can be helpful in interpreting drug screens and ordering specific drug levels or metabolites that can aid in patient management.

In the case of a neglected or allegedly abused child, a positive toxicology screen can add substantial weight to a claim of abuse or neglect. In these cases and any case with medicolegal implications, any positive screen must be confirmed with gas chromatography/mass spectrometry, which is considered the gold standard measurement for legal purposes.

Acetaminophen is a widely available medication and a commonly detected coingestant with the potential for severe toxicity. There is an effective antidote to acetaminophen poisoning that is time-dependent. Given that patients might initially be asymptomatic and might not report acetaminophen as a coingestant, an acetaminophen level should be checked in all patients who present after an intentional exposure or ingestion. A basic chemistry panel (electrolytes, renal function, glucose) is necessary for all poisoned or potentially poisoned patients. Any patient with acidosis (a low serum bicarbonate level on the serum chemistry panel) must have an anion gap calculated because of the more specific differential diagnoses associated with an elevated anion gap metabolic acidosis. Patients with a known overdose of acetaminophen should have their liver transaminases assessed, as well as an INR (international normalized ratio). A serum creatine kinase level is indicated on any patient with a prolonged “down time” as rhabdomyolysis can result from laying supine on a hard surface without movement for just a few hours. Serum osmolality is only helpful as a surrogate marker for a toxic alcohol exposure if a serum concentration of the alcohol cannot be obtained in a reasonable time frame. A urine pregnancy test is, of course, mandatory for all adolescent female patients. Based on the clinical presentation and the presumed poison, additional lab tests may also be helpful (Table 63-5).

Additional Diagnostic Testing
An electrocardiogram (ECG) is a quick and noninvasive bedside test that can yield important clues to diagnosis and prognosis. Toxicologists pay particular attention to the ECG intervals (Table 63-6). A widened QRS interval, putting the patient at risk for monomorphic ventricular tachycardia, suggests blockade of fast sodium channels, and may be seen after ingestion of tricyclic antidepressants, diphenhydramine, and cocaine, among others. A widened QTc interval suggests effects at the potassium rectifier channels and portends a risk of torsades de pointes (polymorphic ventricular tachycardia).
Table 63-2  Selected Historical and Physical Findings in Poisoning

<table>
<thead>
<tr>
<th>SIGN</th>
<th>TOXIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>ODOR</td>
<td></td>
</tr>
<tr>
<td>Bitter almonds</td>
<td>Cyanide, isopropl alcohol, methanol, paraldehyde, salicylates</td>
</tr>
<tr>
<td>Acetone</td>
<td>Ethanol</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Methyl salicylate</td>
</tr>
<tr>
<td>Wintergreen</td>
<td>Arsenic, thallium, organophosphates, selenium</td>
</tr>
<tr>
<td>Garlic</td>
<td></td>
</tr>
<tr>
<td>OCULAR SIGNS</td>
<td></td>
</tr>
<tr>
<td>Miosis</td>
<td>Opioids (except propoxyphene, meperidine, and pentazocine), organophosphates, other cloninergics, clonine, phenothiazines, sedative–hypnotics, olanzapine</td>
</tr>
<tr>
<td>Mydriasis</td>
<td>Anticholinergics (e.g., antihistamines, TCAs, atropine), sympathomimetics (coca, amphetamines, PCP)</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>Anticonvulsants, sedative–hypnotics, alcohols, PCP, ketamine, dextromethorphan</td>
</tr>
<tr>
<td>Lacrimation</td>
<td>Organophosphates, irritant gas or vapors</td>
</tr>
<tr>
<td>Retinal hyperemia</td>
<td>Methanol</td>
</tr>
<tr>
<td>CUTANEOUS SIGNS</td>
<td></td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>Cholinergics (organophosphates), sympathomimetics, withdrawal syndromes</td>
</tr>
<tr>
<td>Alopecia</td>
<td>Thallium, arsenic</td>
</tr>
<tr>
<td>Erythema</td>
<td>Boric acid, elemental mercury, cyanide, carbon monoxide, disulfiram, scombroid, anticholinergics, vancomycin</td>
</tr>
<tr>
<td>Cyanosis (unresponsive to oxygen)</td>
<td>Methemoglobinemia (e.g., benzocaine, dapsone, nitrites, phenazopyridine), amiodarone, silver</td>
</tr>
<tr>
<td>ORAL SIGNS</td>
<td></td>
</tr>
<tr>
<td>Salivation</td>
<td>Organophosphates, salicylates, corrosives, ketamine, PCP, strychnine</td>
</tr>
<tr>
<td>Oral burns</td>
<td>Lead, mercury, arsenic, bismuth</td>
</tr>
<tr>
<td>Gum lines</td>
<td>Lead, mercury, arsenic, bismuth</td>
</tr>
<tr>
<td>GASTROINTESTINAL SIGNS</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Antimicrobials, arsenic, iron, boric acid, cholinergics, colchicine, opioid withdrawal</td>
</tr>
<tr>
<td>Hematemesis</td>
<td>Arsenic, iron, caustics, NSAIDs, salicylates</td>
</tr>
<tr>
<td>Constipation</td>
<td>Lead</td>
</tr>
<tr>
<td>CARDIAC SIGNS</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Sympathomimetics, anticholinergics, antidepressants, antipsychotics, methylxanthenes (theophylline, caffeine), salicylates, cellular asphyxiants (cyanide, carbon monoxide, hydrogen sulfide), withdrawal (ethanol, sedatives, clonine, opioids), serotonin syndrome, neuroleptic malignant syndrome</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>β Blockers, calcium channel blockers, digoxin, clonine, organophosphates, opioids, sedative–hypnotics</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Sympathomimetics, anticholinergics, monoamine oxidase inhibitors, serotonin syndrome, neuroleptic malignant syndrome, clonidine withdrawal</td>
</tr>
<tr>
<td>Hypotension</td>
<td>β Blockers, calcium channel blockers, cyclic antidepressants, iron, antipsychotics, barbiturates, clonine, opioids, arsenic, amatoxin mushrooms, cellular asphyxiants (cyanide, carbon monoxide, hydrogen sulfide), snake envenomation</td>
</tr>
<tr>
<td>RESPIRATORY SIGNS</td>
<td></td>
</tr>
<tr>
<td>Depressed respirations</td>
<td>Opioids, sedative-hypnotics, alcohol, clonidine, barbiturates</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>Salicylates, sympathomimetics, caffeine, metabolic acidosis, carbon monoxide, hydrocarbon aspiration</td>
</tr>
<tr>
<td>CENTRAL NERVOUS SYSTEM SIGNS</td>
<td></td>
</tr>
<tr>
<td>Ataxia</td>
<td>Alcohols, anticonvulsants, sedative–hypnotics, lithium, dextromethorphan, carbon monoxide, inhalants</td>
</tr>
<tr>
<td>Coma</td>
<td>Opioids, sedative-hypnotics, anticonvulsants, antidepressants, antipsychotics, ethanoll, anticholinergics, clonine, GHB, alcohols, salicylates, barbiturates</td>
</tr>
<tr>
<td>Seizures</td>
<td>Sympathomimetics, anticholinergics, antidepressants (especially TCAs, bupropion, venlafaxine), cholinergics (organophosphates), isoniazid, camphor, lindane, salicylates, lead, nicotine, tramadol, water hemlock, withdrawal</td>
</tr>
<tr>
<td>Delirium/psychosis</td>
<td>Sympathomimetics, anticholinergics, LSD, PCP, hallucinogens, lithium, dextromethorphan, steroids, withdrawal</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Lead, arsenic, mercury, organophosphates</td>
</tr>
</tbody>
</table>

GHB, γ-hydroxybutyrate; LSD, lysergic acid diethylamide; NSAID, nonsteroidal antiinflammatory drug; PCP, phencyclidine; TCA, tricyclic antidepressant.

Chest x-ray may reveal signs of pneumonitis (e.g., hydrocarbon aspiration), noncardiogenic pulmonary edema (e.g., salicylate toxicity), or a foreign body. Abdominal x-ray is most helpful in screening for the presence of lead paint chips or other foreign bodies. It may detect a bezoar, demonstrate radiopaque tablets, or reveal drug packets in a body packer. Upper endoscopy may be useful for prognosis after significant caustic ingestions. Further diagnostic testing is based on the differential diagnosis and pattern of presentation.

**PRINCIPLES OF MANAGEMENT**

The principles of management of the poisoned patient are supportive care, antidotes, decontamination, and enhanced elimination. Few patients meet criteria for all of these interventions, though clinicians should consider each option in every poisoned patient so as not to miss a potentially lifesaving therapy. Antidotes are available for relatively few poisons (Table 63-7), thus emphasizing the importance of meticulous supportive care and close clinical monitoring.

Poison control center staff are specifically trained to provide expertise in the management of poisoning exposures. Parents should be instructed to call the poison control center (1-800-222-1222) for any concerning exposure. Poison specialists can assist parents in assessing the potential toxicity and severity of the exposure; they can further determine which children can be safely monitored at home and which children should be referred to the emergency department for further evaluation.
## Recognizable Poison Syndromes ("Toxidromes")

<table>
<thead>
<tr>
<th>TOXIDROME</th>
<th>SIGNS</th>
<th>POSSIBLE TOXINS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathomimetic</td>
<td>Hypertension, tachycardia, hyperthermia</td>
<td>Amphetamines, cocaine, PCP, bath salts, cathinones, ADHD medication</td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>Bradycardia, BP and temp typically normal, HR normal to decreased</td>
<td>Anticholinesterases, muscarinic agonists, atropine, physostigmine</td>
</tr>
<tr>
<td>Cholinergic</td>
<td>Bradycardia, BP and temp typically normal, HR normal to decreased</td>
<td>Organophosphates (insecticides, nerve agents), carbamates, pyridostigmine,筒箭毒碱, antitubercular medications, myasthenia treatments</td>
</tr>
<tr>
<td>Opioids</td>
<td>Respiratory depression, somnolence, coma</td>
<td>Methadone, buprenorphine, morphine, oxycodone, heroin, etc.</td>
</tr>
<tr>
<td>Sedative-hypnotics</td>
<td>Respiratory depression, somnolence, coma</td>
<td>Barbiturates, benzodiazepines, ethanol</td>
</tr>
<tr>
<td>Serotonin syndrome (similar findings with neuroleptic malignant syndrome)</td>
<td>Temperature instability</td>
<td>SSRIs, lithium, MAOIs, inositol, dekemotropin, tramadol, meperidine, dextromethorphan</td>
</tr>
<tr>
<td>Salicylates</td>
<td>Tachycardia, tachypnea, hyperthermia</td>
<td>Aspirin and aspirin-containing products, methyl-salicylate</td>
</tr>
<tr>
<td>Withdrowal (sedative-hypnotic)</td>
<td>Tachycardia, tachypnea, hyperthermia</td>
<td>Lack of access to ethanol, benzodiazepines, barbiturates, excessive use of analgesics</td>
</tr>
<tr>
<td>Withdrowal (opioid)</td>
<td>Tachycardia, tachypnea, hyperthermia</td>
<td>Lack of access to opioids or excessive use of naloxone</td>
</tr>
</tbody>
</table>

**Signs**
- Vital Signs: Agitation, delirium, violence
- Mental Status: Confusion, coma
- Pupils: Dilated, pinpoint
- Skin: Normal to diaphoretic
- Bowel Sounds: Normal, ileus, urinary retention
- Other: Hyperactive, clonic, hyperreflexia (lower extremities > upper extremities)

**Possible Toxins**
- Amphetamines, cocaine, PCP, bath salts, cathinones, ADHD medication
- Anticholinesterases, muscarinic agonists, atropine, physostigmine
- Organophosphates (insecticides, nerve agents), carbamates, pyridostigmine,筒箭毒碱, antitubercular medications, myasthenia treatments
- Methadone, buprenorphine, morphine, oxycodone, heroin, etc.
- Barbiturates, benzodiazepines, ethanol
- SSRIs, lithium, MAOIs, inositol, dekemotropin, tramadol, meperidine, dextromethorphan
- Aspirin and aspirin-containing products, methyl-salicylate
- Lack of access to ethanol, benzodiazepines, barbiturates, excessive use of analgesics
- Lack of access to opioids or excessive use of naloxone

**Notes**
- ABG, arterial blood gas; ADH, attention-deficit/hyperactivity disorder; BP, blood pressure; PCP, phencyclidine; MAO, monoamine oxidase inhibitor; POC, phencyclidine; SSRI, selective serotonin reuptake inhibitor; temp, temperature.
### Table 63-4: Mini-Toxidromes

<table>
<thead>
<tr>
<th>TOXIDROMES</th>
<th>SYMPTOMS AND SIGNS</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>α1 Antagonists</td>
<td>CNS depression, tachycardia, miosis</td>
<td>Chlorpromazine, quetiapine, clozapine, olanzapine, risperidone</td>
</tr>
<tr>
<td>α2 Agonist</td>
<td>CNS depression, bradycardia, hypertension (early), hypotension (late), miosis</td>
<td>Clonidine, oxymetazoline, tetrahydrozoline, tizanidine</td>
</tr>
<tr>
<td>Clonus/myoclonus</td>
<td>CNS depression, myoclonic jerks, clonus, hyperreflexia</td>
<td>Carisoprodol, lithium, serotoninergic agents, bismuth, organic lead, organic mercury</td>
</tr>
<tr>
<td>Sodium channel blockers</td>
<td>CNS toxicity, wide QRS</td>
<td>Cyclic antidepressants and structurally related agents, proproxyphene, quinidine/quinine, amantadine, antihistamines, bupropion, cocaine</td>
</tr>
<tr>
<td>Potassium channel blockers</td>
<td>CNS toxicity, long QT</td>
<td>Butyrophenones, methadone, phenothiazines, ziprasidone</td>
</tr>
</tbody>
</table>

CNS, central nervous system.


### Table 63-5: Screening Laboratory Clues in Toxicologic Diagnosis

<table>
<thead>
<tr>
<th>ANION GAP METABOLIC ACIDOSIS (MNEMONIC = MUDPILES CAT)</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol, metformin</td>
<td></td>
</tr>
<tr>
<td>Uremia</td>
<td></td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td></td>
</tr>
<tr>
<td>Propylene glycol</td>
<td></td>
</tr>
<tr>
<td>Isoniazid, iron, massive ibuprofen</td>
<td></td>
</tr>
<tr>
<td>Lactic acidosis</td>
<td></td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td></td>
</tr>
<tr>
<td>Salicylates</td>
<td></td>
</tr>
<tr>
<td>Cellular asphyxiants (cyanide, carbon monoxide, hydrogen sulfide)</td>
<td></td>
</tr>
<tr>
<td>Alcoholic ketoacidosis</td>
<td></td>
</tr>
<tr>
<td>Tylenol</td>
<td></td>
</tr>
<tr>
<td>ELEVATED OSMOLAR GAP</td>
<td></td>
</tr>
<tr>
<td>Alcohols: ethanol, isopropyl, methanol, ethylene glycol</td>
<td></td>
</tr>
<tr>
<td>HYPOGLYCEMIA (MNEMONIC = HOBBIES)</td>
<td></td>
</tr>
<tr>
<td>Hypoglycemics, oral: sulfonylureas, meglitindes</td>
<td></td>
</tr>
<tr>
<td>Other: quinine, unripe ackee fruit</td>
<td></td>
</tr>
<tr>
<td>Beta Blockers</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
</tr>
<tr>
<td>Ethanol</td>
<td></td>
</tr>
<tr>
<td>Salicylates (late)</td>
<td></td>
</tr>
<tr>
<td>HYPERGLYCEMIA</td>
<td></td>
</tr>
<tr>
<td>Salicylates (early)</td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td></td>
</tr>
<tr>
<td>Caffeine</td>
<td></td>
</tr>
<tr>
<td>HYPOCALCEMIA</td>
<td></td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td></td>
</tr>
<tr>
<td>Fluoride</td>
<td></td>
</tr>
<tr>
<td>RHABDOMYOLYSIS</td>
<td></td>
</tr>
<tr>
<td>Neuroleptic malignant syndrome, serotonin syndrome</td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td></td>
</tr>
<tr>
<td>Mushrooms (Tricholoma equestre)</td>
<td></td>
</tr>
<tr>
<td>Any toxin causing prolonged immobilization (e.g., opioids, antipsychotics) or excessive muscle activity or seizures (e.g., sympathomimetics)</td>
<td></td>
</tr>
<tr>
<td>RADIOPAQUE SUBSTANCE ON KUB (MNEMONIC = CHIPPED)</td>
<td></td>
</tr>
<tr>
<td>Chloral hydrate, calcium carbonate</td>
<td></td>
</tr>
<tr>
<td>Heavy metals (lead, zinc, barium, arsenic, lithium, bismuth)</td>
<td></td>
</tr>
<tr>
<td>Iron</td>
<td></td>
</tr>
<tr>
<td>Phenothiazines</td>
<td></td>
</tr>
<tr>
<td>Play-Doh, potassium chloride</td>
<td></td>
</tr>
<tr>
<td>Enteric-coated pills</td>
<td></td>
</tr>
<tr>
<td>Dental amalgam, drug packets</td>
<td></td>
</tr>
</tbody>
</table>

KUB, kidney-ureter-bladder radiograph.

### Table 63-6: Electrocardiographic Findings in Poisoning

<table>
<thead>
<tr>
<th>PR INTERVAL PROLONGATION</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td></td>
</tr>
<tr>
<td>QRS PROLONGATION</td>
<td></td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td></td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
</tr>
<tr>
<td>Cardiac glycosides</td>
<td></td>
</tr>
<tr>
<td>Chloroquine, hydroxylchloroquine</td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td></td>
</tr>
<tr>
<td>Quinidine, quinine, procainamide, disopyramide</td>
<td></td>
</tr>
<tr>
<td>Phenothiazines</td>
<td></td>
</tr>
<tr>
<td>Propoxyphene</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td></td>
</tr>
<tr>
<td>Bupropion, venlafaxine</td>
<td></td>
</tr>
<tr>
<td>ELEVATED OSMOLAR GAP</td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td></td>
</tr>
<tr>
<td>Antipsychotics (typical and atypical)</td>
<td></td>
</tr>
<tr>
<td>Arsenic</td>
<td></td>
</tr>
<tr>
<td>Cisapride</td>
<td></td>
</tr>
<tr>
<td>Citalopram and other SSRIs</td>
<td></td>
</tr>
<tr>
<td>Clarithromycin, erythromycin</td>
<td></td>
</tr>
<tr>
<td>Disopyramide, dofetilide, ibutilide</td>
<td></td>
</tr>
<tr>
<td>Fluconazole, ketoconazole, itraconazole</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td></td>
</tr>
<tr>
<td>Pentamidine</td>
<td></td>
</tr>
<tr>
<td>Phenothiazines</td>
<td></td>
</tr>
<tr>
<td>Sotalol</td>
<td></td>
</tr>
</tbody>
</table>

*This is a select list of important toxins, other medications are also associated with QTc prolongation.

SSRI, selective serotonin reuptake inhibitor.

evaluation and care. Ninety percent of all exposures in children younger than 6 yr of age called into poison centers are managed at home. The American Academy of Clinical Toxicology has generated consensus statements for out-of-hospital management of common ingestions (e.g., acetaminophen, iron, calcium channel blockers) that serve to guide poison center recommendations regarding whom to refer to an emergency department. Up to a third of calls to poison centers involve hospitalized patients.

### SUPPORTIVE CARE

Careful attention is paid first to the “ABCs” of airway, breathing and circulation; there should be a low threshold to aggressively manage the airway of a poisoned patient because of the patient’s propensity to
<table>
<thead>
<tr>
<th>POISON</th>
<th>ANTIDOTE</th>
<th>DOSAGE</th>
<th>ROUTE</th>
<th>ADVERSE EFFECTS, WARNINGS, COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>N-Acetylcysteine (Mucomyst)</td>
<td>140 mg/kg loading, followed by 70 mg/kg q4h</td>
<td>PO</td>
<td>Vomiting (patient-tailored regimens are the norm) Anaphylactoid reactions (most commonly seen with loading dose) (Higher doses of the infusion are often recommended depending upon the acetaminophen level and the degree of injury)</td>
</tr>
<tr>
<td></td>
<td>N-Acetylcysteine (Acetaclote)</td>
<td>150 mg/kg over 1 hr, followed by 50 mg/kg over 4 hr, followed by 100 mg/kg over 16 hr</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Physostigmine</td>
<td>0.02 mg/kg over 5 min; may repeat q5-10min to 2 mg max</td>
<td>IV/IM</td>
<td>Bradycardia, seizures, bronchospasm Note: Do not use if conduction delays on ECG</td>
</tr>
<tr>
<td>Benzodiazipines</td>
<td>Flumazenil</td>
<td>0.2 mg over 30 sec; if response is inadequate, repeat q1min to 1 mg max</td>
<td>IV</td>
<td>Agitation, seizures; do not use for unknown ingestions</td>
</tr>
<tr>
<td>β Blockers</td>
<td>Glucagon</td>
<td>0.15 mg/kg bolus followed by infusion of 0.05-0.15 mg/kg/hr</td>
<td>IV</td>
<td>Hyperglycemia, vomiting</td>
</tr>
<tr>
<td>Calcium channel</td>
<td>Insulin</td>
<td>1 unit/kg bolus followed by infusion of 0.5-1 unit/kg/hr</td>
<td>IV</td>
<td>Hypoglycemia Follow serum potassium and glucose closely</td>
</tr>
<tr>
<td>blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium salts</td>
<td></td>
<td>Dose depends on the specific calcium salt</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>Oxygen</td>
<td>100% FIO₂ via non-rebreather mask (or ET if intubated)</td>
<td>Inhalational</td>
<td>Some patients may benefit from hyperbaric oxygen (see text)</td>
</tr>
<tr>
<td>Cyanide</td>
<td>Cyanide kit: Amyl nitrate</td>
<td>1 crushable ampule; inhale 30 sec of each min</td>
<td>Inhalation</td>
<td>Methemoglobinemia</td>
</tr>
<tr>
<td></td>
<td>Sodium nitrate</td>
<td>0.33 mL/kg of 3% solution if hemoglobin level is not known; otherwise, based on tables with product</td>
<td>IV</td>
<td>Methemoglobinemia Hypotension</td>
</tr>
<tr>
<td></td>
<td>Sodium thiosulfate</td>
<td>1.6 mL/kg of 25% solution; may be repeated q30-60min to max of 50 mL</td>
<td>IV</td>
<td>If inducing methemoglobinemia is contraindicated; consider only using the thiosulfate component of the kit Flushing/erythema, nausea, rash, chromaturia, hypertension, headache</td>
</tr>
<tr>
<td></td>
<td>Hydroxocobalamin (Cyanokit)</td>
<td>70 mg/kg (adults: 5 g) given over 15 min</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>Digitalis</td>
<td>Digoxin-specific Fab antibodies (Digibind; DigiFab)</td>
<td>1 vial binds 0.6 mg of digitalis glycoside; #vials = digitalis level x weight in kg/100</td>
<td>IV</td>
<td>Allergic reactions (rare), return of condition being treated with digitalis glycoside</td>
</tr>
<tr>
<td>Ethylene glycol,</td>
<td>Fomepizole</td>
<td>15 mg/kg load; 10 mg/kg q12h x 4 doses; 15 mg/kg q12h until EG level is &lt;20 mg/dL</td>
<td>IV</td>
<td>Infuse slowly over 30 min; If fomepizole is not available, can treat with oral ethanol (80 proof)</td>
</tr>
<tr>
<td>methanol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron</td>
<td>Deferoxamine</td>
<td>Infusion of 5-15 mg/kg/hr (max: 6 g/24 hr)</td>
<td>IV</td>
<td>Hypotension (minimized by avoiding rapid infusion rates)</td>
</tr>
<tr>
<td>Isoniazid (INH)</td>
<td>Pyridoxine</td>
<td>Empirical dosing: 70 mg/kg (max dose = 5 g) If ingested dose is known: 1 g per gram of INH</td>
<td>IV</td>
<td>May also be used for Gyromitra mushroom ingestions</td>
</tr>
<tr>
<td>Lead and other</td>
<td>BAL (dimercaprol)</td>
<td>3-5 mg/kg/dose q4hr, for the 1st day; subsequent dosing depends on the toxin</td>
<td>Deep IM</td>
<td>Local injection site pain and sterile abscess, vomiting, fever, salivation, nephrotoxicity Caution: prepared in peanut oil; contraindicated in patients with peanut allergy Vomiting, fever, hypertension, arthralgias, allergic reactions, local inflammation, nephrotoxicity (maintain adequate hydration, follow UA and renal function) Vomiting, hepatic transaminase elevation, rash</td>
</tr>
<tr>
<td>heavy metals (e.g.,</td>
<td>Calcium disodium EDTA</td>
<td>35-50 mg/kg/day x 5 days; may be given as a continuous infusion or 2 divided doses/day</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>arsenic, inorganic</td>
<td>Dimercaptosuccinic acid (succimer, DMSA, Chemet)</td>
<td>10 mg/kg/dose q8h x 5 days, then 10 mg/kg q12h x 14 days</td>
<td>PO</td>
<td></td>
</tr>
<tr>
<td>mercury)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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</table>
quickly become comatose. In fact, endotracheal intubation is often the only significant intervention needed in many poisoned patients, especially those poisoned with neuroleptics. An important caveat is with the tachypneic patient with a clear lung exam and normal oxygen saturation. This should alert the clinician to the likelihood that the patient is compensating for an acidemia. Paralyzing such a patient and ventilating them might prove fatal. If intubation is absolutely necessary for airway protection or a tiring patient, a good rule of thumb is to match the ventilatory settings to the patient’s preintubation minute ventilation.

In the hypotensive patient, it should be remembered that these patients often are not hypovolemic, but are poisoned; aggressive fluid resuscitation may lead to fluid overload. If hypotension persists after 1 or 2 standard boluses of crystalloid, infusion of a direct-acting vasoconstrictor, such as norepinephrine or epinephrine, is preferred. Dysrhythmias are managed in the standard fashion apart from those caused by agents that block the fast sodium channels of the heart for which sodium bicarbonate therapy is utilized.

Seizures are primarily managed with agents that potentiate the γ-aminobutyric acid complex, such as benzodiazepines or barbiturates. Creatinine kinase levels should be drawn on any patient found unconscious. The goal of supportive therapy is to support the patient’s vital functions until the patient can eliminate the toxin.

### Antidotes

Antidotes are available for relatively few toxins (see Tables 63-7 and 63-8), but early and appropriate use of an antidote is a key element in managing the poisoned patient.

### Decontamination

The majority of poisonings in children are from ingestion, although exposures can also occur via inhalational, dermal, and ocular routes. The goal of decontamination is to minimize absorption of the toxic substance. The specific method employed depends on the properties of the toxin itself and the route of exposure. Regardless of the decontamination method used, the efficacy of the intervention decreases with increasing time since exposure. Decontamination should not be routinely employed for every poisoned patient. Instead, careful decisions regarding the utility of decontamination should be made for each patient and should include consideration of the toxicity and pharmacologic properties of the exposure, the route of the exposure, the time since the exposure, and the risks vs the benefits of the decontamination method.

Dermal and ocular decontamination begin with removal of any contaminated clothing and particulate matter, followed by flushing of the affected area with tepid water or normal saline. Treatment clinicians should wear proper protective gear when performing irrigation. Flushing for a minimum of 10-20 minutes is recommended for most exposures, although some chemicals (e.g., alkaline corrosives) require much longer periods of flushing. Dermal decontamination, especially after exposure to adherent or lipophilic (e.g., organophosphates) agents, should include thorough cleansing with soap and water. Water should not be used for decontamination after exposure to highly reactive agents, such as elemental sodium, phosphorus, calcium oxide, and titanium tetrachloride. After an inhalational
Gastrointestinal (GI) decontamination is a controversial topic among medical toxicologists. GI decontamination strategies are most likely to be effective in the 1st hour after an acute ingestion. GI absorption may be delayed after ingestion of agents that slow GI motility (anticholinergic medications, opioids), massive pill ingestions, sustained-release preparations, and ingestions of agents that can form pharmacologic bezoars (e.g., enteric-coated salicylates). GI decontamination at more than 1 hr after ingestion may be considered in patients who ingest toxic substances with these properties. Even rapid institution of GI decontamination with activated charcoal will, at best, bind only approximately 30% of the ingested substance. GI decontamination should never supplant excellent supportive care and should not be employed in an unstable or persistently vomiting patient. Described methods of GI decontamination include induced emesis with ipecac, gastric lavage, cathartics, activated charcoal, and whole-bowel irrigation (WBI). Of these, only activated charcoal and WBI are likely to be of clinical benefit.

**Syrup of Ipecac**

Syrup of ipecac contains 2 emetic alkaloids that work in both the central nervous system (CNS) and locally in the GI tract to produce vomiting. In the 1960s, the American Academy of Pediatrics lobbied for nonprescription availability of ipecac and in the 1980s recommended that ipecac be given to parents at the 6 mo well-child check, coupled with a discussion about poison prevention strategies. Since then, studies have failed to document a significant clinical impact from the use of ipecac and have documented multiple adverse events from its use. After a review of the evidence and assessment of the risks and benefits of ipecac use, the American Academy of Pediatrics, the American Academy of Clinical Toxicology, and the American Association of Poison Control Centers have all published statements in favor of abandoning the use of ipecac.

**Gastric Lavage**

Gastric lavage involves placing a tube into the stomach to aspirate contents, followed by flushing with aliquots of fluid, usually water or normal saline. Although gastric lavage was used routinely for many years, objective data do not document or support clinically relevant efficacy. This is particularly true in children, in whom only small-bore tubes can be used. Lavage is time-consuming and painful, and can induce bradycardia via a vagal response to tube placement. It can delay administration of more definitive treatment (activated charcoal), and under the best circumstances only removes a fraction of gastric contents. Thus, in most clinical scenarios, the use of gastric lavage is no longer recommended.

**Single-Dose Activated Charcoal**

Activated charcoal is thought to be a potentially useful method of GI decontamination, although clinical data to support this claim is limited. Charcoal is “activated” via heating to extreme temperatures, creating an extensive network of pores that provides a very large adsorptive surface area. Many, but not all, toxins are adsorbed onto its surface, thus preventing absorption from the GI tract. Charcoal is most likely to be effective when given within 1 hr of ingestion. Charged molecules (i.e., heavy metals, lithium, iron) and liquids do not bind well to activated charcoal (Table 63-9). Charcoal administration should also be avoided after ingestion of a caustic substance, because the presence of charcoal can impede subsequent endoscopic evaluation. A repeat dose of activated charcoal may be warranted in the cases of ingestion of an extended release product or, more commonly, with a significant salicylate poisoning as a result of its delayed and erratic absorption pattern.

The dose of activated charcoal is 1 g/kg in children or 50–100 g in adolescents and adults. Before administering charcoal, one must ensure that the patient’s airway is intact or protected and that the patient has a benign abdominal exam. In the awake, uncooperative adolescent or child who refuses to drink the activated charcoal, there is relatively little utility and potential morbidity associated with forcing activated charcoal down a nasogastric tube, and such practice should be avoided. Approximately 20% of children vomit after receiving a dose of charcoal, emphasizing the importance of an intact airway and avoiding administration of charcoal after ingestion of substances that are particularly toxic when aspirated (e.g., hydrocarbons). If charcoal is given through a gastric tube in an intubated patient, placement of the tube should be carefully confirmed before activated charcoal is given because instillation of charcoal directly into the lungs can have disastrous effects. Constipation is another common side effect of activated charcoal, and in rare cases, bowel perforation has been reported.

In young children, practitioners may attempt to improve palatability by adding flavorings (chocolate or cherry syrup) or giving the mixture over ice cream. Cathartics (sorbitol, magnesium sulfate, magnesium citrate) have been used in conjunction with activated charcoal to prevent constipation and accelerate evacuation of the charcoal–toxin complex. There are no data demonstrating their value and there are numerous reports of adverse effects from cathartics. Cathartics should be used with care in young children and should never be used in multiple doses because of the risk of dehydration and electrolyte imbalance.

**Whole-Bowel Irrigation**

WBI involves instilling large volumes (35 mL/kg/hr in children or 1–2 L/hr in adolescents) of a polyethylene glycol electrolyte solution (e.g., GoLYTELY) to “wash out” the entire GI tract. This technique may have some success after the ingestion of slowly absorbed substances (sustained-release preparations), substances not well adsorbed by charcoal (e.g., lithium, iron), transdermal patches, and drug packets. WBI can be combined with the use of activated charcoal, if appropriate (cocaïne or heroin body packers). In children, WBI is of greatest utility in decontaminating the gut of a child whose abdominal X-ray demonstrates multiple lead paint chips. Careful attention should be paid to assessment of the airway and abdominal exam before initiating WBI, which should never be given to a patient without bowel sounds or with signs of obstruction or ileus, or without a protected airway. Given the rate of administration and volume needed to flush the system, WBI is typically administered via a nasogastric tube. WBI is continued until the rectal effluent is clear. Complications of WBI include vomiting, abdominal pain, and abdominal distention. Bezoar formation might respond to WBI but may also require endoscopy or surgery.

**Enhanced Elimination**

Enhancing excretion is only useful for a few toxins; in these cases, enhancing elimination is a potentially lifesaving intervention that results in improved clearance of a poison that has already been absorbed.

**Urinary Alkalization**

A charged molecule, being polar and hydrophilic, does not easily cross a fat membrane. Such is the mechanism by which alkalinizing the urine enhances the elimination of some drugs that are weak acids by forming charged particles that are “trapped” within the renal tubules and thus excreted. Urinary alkalinization is accomplished via a continuous infusion of sodium bicarbonate—containing intravenous fluids, with a goal urine pH of 7.5–8. Alkalinization of the urine is most useful in managing salicylate and methotrexate toxicity.

Serum pH should be closely monitored because a serum pH of >7.55 is potentially dangerous to cellular functions. Other complications of

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**Table 63-9** Substances Poorly Adsorbed By Activated Charcoal

<table>
<thead>
<tr>
<th>Substance</th>
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<tbody>
<tr>
<td>Alcohols</td>
</tr>
<tr>
<td>Caustics: alkalis and acids</td>
</tr>
<tr>
<td>Cyanide</td>
</tr>
<tr>
<td>Heavy metals (e.g., lead)</td>
</tr>
<tr>
<td>Hydrocarbons</td>
</tr>
<tr>
<td>Iron</td>
</tr>
<tr>
<td>Lithium</td>
</tr>
</tbody>
</table>

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**Lithium**

Lithium

Heavy metals (e.g., lead)

Cyanide

Caustics: alkalis and acids

Alcohols

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urinary alkalinitization include electrolyte derangements, such as hypo-
kalemia and hypocalcemia. This method of enhanced elimination is con-traindicated in patients who are unable to tolerate the large volumes of fluid needed to achieve alkalinitization, including patients with heart failure, kidney failure, pulmonary edema, or cerebral edema.

Hemodialysis
Few drugs or toxins are removed by dialysis in amounts sufficient to justify the risks and difficulty of dialysis. Toxins that are amenable to dialysis have the following properties: low volume of distribution (<1 L/kg), low molecular weight, low degree of protein binding, and high degree of water solubility. Examples of toxins for which dialysis may be useful include methanol, ethylene glycol, salicylates, theophylline, bromide, lithium, and, potentially, valproic acid. In addition to enhancing the elimination of the toxin itself, hemodialysis can also be useful to correct severe electrolyte disturbances and acid-base derange-
ments resulting from the ingestion (e.g., metformin-associated lactic acidosis).

Multiple-Dose Activated Charcoal
Whereas single-dose activated charcoal is used as a method of decon-
tamination, multiple doses of activated charcoal (MDACs) can help to enhance the elimination of some toxins. MDAC is typically given as 0.5 g/kg every 4-6 hr (for ≤24 hr) and continued until there is significant clinical improvement, including satisfactory decline of serum drug concentrations. MDACs enhance elimination via 2 proposed mechanisms: interruption of enterohepatic recirculation and “GI dialy-
sis,” which uses the intestinal mucosa as the dialysis membrane and pulls toxins from the bloodstream back into the intraluminal space, where they are adsorbed to the charcoal. The American Academy of Clinical Toxicology/European Association of Poisons Centres and Clinical Toxicologists position statement recommends MDAC in managing significant ingestions of carbamazepine, dapson, phenobarbital, quinine, and theophylline. As with single-dose activated charcoal, con-
traindications to use of MDAC include an unprotected airway and a concerning abdominal exam (e.g., ileus, distention, peritoneal signs); thus the airway and abdominal exam should be assessed before each dose. A cathartic (e.g., sorbitol) may be given with the first dose, but it should not be used with subsequent doses owing to the risk of dehydra-
tion and electrolyte derangements. Although MDAC reduces the serum level of an intoxicant quicker than without MDAC, it has not been shown to have a significant impact on outcome.

Intralipid Emulsion Therapy
A potentially life-saving intervention of infusing Intralipid emulsions is a means of sequestering fat-soluble drugs and decreasing their impact at target organs. Initial experience regarding this intervention has been developed by anesthesiologists as a reversal agent for asystole resulting from inadvertent intravenous injection of bupivacaine. There are dozens of case reports published demonstrating the dramatic and rapid recovery of premorbid poisoned patients given a dose of Intralipid. Using the same 20% Intralipid used for total parenteral nutrition, a bolus dose of 1.5 mL/kg is given over 3 min, followed by an infusion of 0.25 mL/kg/min until recovery or a total of 10 mL/kg has been infused. Lipophilic drugs (LogP >2) are potentially bound by Intralipid emulsions, including calcium channel blockers (verapamil and diltia-
zem) and tricyclic antidepressants.

SELECTED COMPOUNDS COMMONLY INVOLVED IN PEDIATRIC POISONINGS
Herbal medicines (see Chapter 64), drugs of abuse (see Chapter 114), and environmental health hazards (see Chapters 718-725) are covered elsewhere.

Pharmaceuticals
Analgesics
Acetaminophen. Acetaminophen (APAP) is the most widely used analgesic and antipyretic in pediatrics, available in multiple for-
mulations, strengths, and combinations. Consequently, APAP is com-
monly available in the home, where it can be unintentionally ingested by young children, taken in an intentional overdose by adolescents and adults, or inappropriately dosed in all ages. APAP toxicity remains the most common cause of acute liver failure in the United States, and is the number 1 cause of intentional poisoning death in the United States.

Pathophysiology. APAP toxicity results from the formation of a highly reactive intermediate metabolite, N-acetyl-p-benzoquinone imine. In therapeutic use, only a small percentage of a dose (approximately 5%) is metabolized by the hepatic cytochrome P450 enzyme CYP2E1 to N-acetyl-p-benzoquinone imine, which is then immedi-
ately conjugated with glutathione to form a nontoxic mercapturic acid conjugate. In overdose, glutathione stores are overwhelmed, and free N-acetyl-p-benzoquinone imine is able to combine with hepatic mac-
romolecules to produce hepatocellular necrosis. The single acute toxic dose of APAP is generally considered to be >200 mg/kg in children and >7.5-10 g in adolescents and adults. Repeated administration of APAP at supratherapeutic doses (>90 mg/kg/day for consecutive days) can lead to hepatic injury or failure in some children, especially in the setting of fever, dehydration, poor nutrition, and other conditions that serve to reduce glutathione stores.

Any child with a history of acute ingestion of >200 mg/kg (unusual in children younger than 6 yr old) or with an acute intentional inges-
tion of any amount should be referred to a healthcare facility for clini-
cal assessment and measurement of a serum APAP level.

Clinical and Laboratory Manifestations. Classically, 4 general stages of APAP toxicity have been described (Table 63-10). The initial signs are nonspecific (i.e., nausea and vomiting) and may not be present. Thus, the diagnosis of APAP toxicity cannot be based on clinical symptoms alone, but instead requires consideration of the combina-
tion of the patient’s history, symptoms, and laboratory findings.

If a toxic ingestion is suspected, a serum APAP level should be measured 4 hr after the reported time of ingestion. For patients who present to medical care more than 4 hr after ingestion, a stat APAP level should be obtained. APAP levels obtained <4 hr after ingestion, unless “nondetectable,” are difficult to interpret and cannot be used to estimate the potential for toxicity. Other important baseline labs include hepatic transaminases, renal function tests, and coagulation parameters.

Treatment. When considering the treatment of a patient poi-
soned or potentially poisoned with APAP, and after assessment of the ABCs, it is helpful to place the patient into one of the following 4 categories.

1. Prophylactic: By definition, these patients have a normal aspartate aminotransferase (AST). If the APAP level is known and the ingestion is within 24 hr of the level being drawn, then treatment

<table>
<thead>
<tr>
<th>Table 63-10</th>
<th>Classic Stages in the Clinical Course of Acetaminophen Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAGE</td>
<td>TIME AFTER INGESTION</td>
</tr>
<tr>
<td>I</td>
<td>0.5-24 hr</td>
</tr>
<tr>
<td></td>
<td>Labs typically normal except for acetaminophen level</td>
</tr>
<tr>
<td>II</td>
<td>24-48 hr</td>
</tr>
<tr>
<td>III</td>
<td>3-5 days</td>
</tr>
<tr>
<td>IV</td>
<td>4 days-2 wk</td>
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</table>
decisions are based on where the level falls on the Rumack-Matthew nomogram (Fig. 63-1). Any patient with a serum APAP level in the possible or probable hepatotoxicity range per the nomogram should be treated with N-acetylcysteine (NAC). This nomogram is only intended for use in patients who present within 24 hr of a single acute APAP ingestion with a known time of ingestion. If treatment is recommended, they should receive either oral Mucomyst or IV Acetadote for 24 or 21 hr, respectively. Repeat AST and APAP concentration drawn toward the end of that interval should be obtained. If the AST is normal and the APAP becomes nondetectable, then treatment may be discontinued. If the AST becomes elevated, then the patient moves into the next category of treatment (injury). If APAP is still present, treatment should be continued until the level is nondetectable. In the case of a patient with a documented APAP level, normal AST, and an unknown time of ingestion, treatment should ensue until the level is nondetectable, with normal transaminases.

The importance of instituting therapy with either IV or oral NAC no later than 8 hr from the time of ingestion cannot be overstressed. No patient, no matter the size of the ingestion, who receives NAC within 8 hr of overdose should die from liver failure. The further out from the 8 hr mark the initiation of therapy is delayed, the greater the risk of acute liver failure. Any patient presenting close to that 8 hr mark or beyond it after an APAP overdose should be empirically started on NAC pending lab results.

2. Hepatic Injury: These patients are exhibiting evidence of hepatocellular necrosis, manifested first as elevated liver transaminases (AST rises first, then the alanine aminotransferase), followed by a rise in the INR. Any patient in this category requires therapy with NAC (IV or oral). When to discontinue therapy in the clinically well patient remains controversial, but in general, the transaminases and INR have peaked and fallen significantly “toward” normal (they do not need to be normal). Most patients’ liver enzymes will peak 3 or 4 days after their ingestion.

3. Acute Liver Failure: The King’s College criteria are used to determine which patients should be referred for consideration of liver transplant. These criteria include acidemia (serum pH < 7.3) after adequate fluid resuscitation, coagulopathy (INR > 6), renal dysfunction (creatinine > 3.4 mg/dL), and grade III or IV hepatic encephalopathy (see Chapter 364). A serum lactate > 3 mmol/L (after IV fluids) adds to both the sensitivity and specificity of the criteria to predict death without liver transplant. The degree of transaminase elevation does not factor in to this decision making process.

4. Repeated Supratherapeutic Ingestion: APAP is particularly prone to unintentional overdose through the ingestion of multiple medications containing the drug or simply because people assume it to be safe at any dose. Ingestion of amounts significantly greater than the recommended daily dose for several days or more puts one at risk for liver injury. Because the Rumack-Matthew nomogram is not helpful in this scenario, a conservative approach is in order. In the asymptomatic patient, if the AST is normal and the APAP is < 10 µg/mL, then no therapy is indicated. A normal AST and an elevated APAP warrants NAC dosing for at least long enough for the drug to metabolize while the AST remains normal. An elevated AST puts the patient in the “hepatic injury” category described above. A patient presenting with symptoms (i.e., right upper quadrant pain, vomiting, jaundice) should be empirically started on NAC pending lab results.

NAC is available in oral and intravenous forms, and both are equally efficacious (see Table 63-7 for the dosing regimens of the oral vs IV form). The intravenous form is used in patients with intractable vomiting, those with evidence of hepatic failure, and pregnant patients. Oral NAC has an unpleasant taste and smell, and can be mixed in soft drink or fruit juice or given via nasogastric tube to improve tolerability of the oral regimen. Administration of IV NAC (as a standard 3% solution to avoid administering excess free water, typically in 5% dextrose), especially the initial loading dose, is associated in some patients with the development of anaphylactoid reactions (non–immunoglobulin E mediated). These reactions are typically managed by stopping the infusion; treating with diphenhydramine, albuterol, and/or epinephrine as indicated; and restarting the infusion at a slower rate once symptoms have resolved. IV NAC is also associated with mild elevation in measured INR (range: 1.2-1.5). IV dosing does, however, deliver less drug to the liver compared with the oral regimen. As a result, many toxicologists now recommend higher doses of the IV formulation in patients with large overdoses.

Transaminases, synthetic function, and renal function should be followed daily while the patient is being treated with NAC. Patients with worsening hepatic function or clinical status might benefit from more frequent lab monitoring. A patient-tailored approach is the norm for when to stop NAC therapy, for deciding whom to refer for transplantation evaluation, and often for the dose of IV NAC in patients with either very high APAP levels or signs of significant injury. Consultation with the regional poison center and medical toxicologist can help streamline the care of these patients, ultimately shortening their length of stay with potentially improved outcomes.

Salicylates. The incidence of salicylate poisoning in young children has declined dramatically since APAP and ibuprofen replaced aspirin as the most commonly used analgesics and antipyretics in
Pathophysiology. Salicylates lead to toxicity by interacting with a wide array of physiologic processes, including direct stimulation of the respiratory center, uncoupling of oxidative phosphorylation, inhibition of the tricarboxylic acid cycle, and stimulation of glycolysis and gluconeogenesis. The acute toxic dose of salicylates is generally considered to be >150 mg/kg. More significant toxicity is seen after ingestions of >300 mg/kg, and severe, potentially fatal, toxicity is described after ingestions of >500 mg/kg.

Clinical and Laboratory Manifestations. Salicylate ingestions are classified as acute or chronic, and acute toxicity is far more common in pediatric patients. Early signs of acute salicylism include nausea, vomiting, diaphoresis, and tinnitus. Moderate salicylate toxicity can manifest as tachypnea and hyperpnea, tachycardia, and altered mental status. The tachycardia results in large part from marked insensible losses from vomiting, tachypnea, diaphoresis, and uncoupling of oxidative phosphorylation. Thus, careful attention should be paid to volume status and early volume resuscitation in the significantly poisoned patient. Signs of severe salicylate toxicity include hyperthermia, coma, and seizures. Chronic salicylism can have a more insidious presentation, and patients can show marked toxicity at significantly lower salicylate levels than in acute toxicity.

Classically, lab values from a patient poisoned with salicylates reveal a primary respiratory alkalosis and a primary, elevated anion gap, metabolic acidosis. Early in the course of acute salicylism, respiratory alkalosis dominates. As the respiratory stimulation diminishes, the patient will move toward the metabolic acidosis. Hyperglycemia (early) and hypoglycemia (late) have been described. Abnormal coagulation studies and acute kidney injury may be seen but are not common.

Serial serum salicylate levels should be closely monitored (every 2-3 hr initially) until they are consistently down trending. Salicylate absorption in overdose is often unpredictable and erratic, especially with an enteric coated product, and levels can rapidly increase into the highly toxic range, even many hours after the ingestion. The Done nomogram is of poor value and should not be used. Serum and urine pH and electrolytes should be followed closely. An APAP level should be checked in any patient who intentionally overdoses on salicylates, because APAP is a common coingestant and because people often confuse or combine their nonprescription analgesics and electrolyte supplements. Salicylate toxicity can cause a noncardiogenic pulmonary edema, especially in chronic overdose; consequently, a chest x-ray is recommended in any patient in respiratory distress.

Treatment. For the patient who presents soon after an acute ingestion, initial treatment should include gastric decontamination with activated charcoal. Salicylate pills occasionally form concretions in the gastrointestinal tract, and abdominal pain. Although GI bleeding and ulcers have been described with chronic use, they are rare in the setting of acute ingestion. After massive ingestions, patients can develop marked CNS depression, anion gap metabolic acidosis, renal insufficiency, and (rarely) respiratory depression. Seizures have also been described, especially after overdose of mefenamic acid. Specific drug levels are not readily available nor do they inform management decisions. Renal function studies, acid–base balance, complete blood count, and coagulation parameters should be monitored after very large ingestions.

Oral Opioids. Opioids are a commonly abused class of medications (see Chapter 114), both in their IV and oral forms. Two specific...
oral opioids, buprenorphine and methadone, merit particular mention because of potential life-threatening toxicity in toddlers with ingestion of even 1 pill. Both agents are used in managing opioid dependence, although buprenorphine is the drug of choice. Methadone is also widely used in the treatment of chronic pain, meaning multiday prescriptions can be filled. Both drugs are readily available for illicit purchase and potential abuse. Both drugs are of great potential toxicity to a toddler, especially buprenorphine, owing to its long half-life and high potency.

Pathophysiology. Methadone is a lipophilic synthetic opioid with potent agonist effects at μ-opioid receptors, leading to both its desired analgesic effects and undesired side effects, including sedation, respiratory depression, and impaired GI motility. Methadone is thought to cause QTc interval prolongation via interactions with the human ether-a-go-go–related gene (hERG)-encoded potassium rectifier channel. Methadone has an average half-life of >25 hr, which may be extended to >50 hr in overdose.

Suboxone is a combination of buprenorphine, a potent opioid with partial agonism at μ-opioid receptors and weak antagonism at κ-opioid receptors, and naloxone. Naloxone has poor oral bioavailability but is included in the formulation to discourage diversion for intravenous use, during which it can precipitate withdrawal. Suboxone is formulated for buccal or sublingual administration; consequently, toddlers can absorb significant amounts of drug even by sucking on a tablet. Buprenorphine has an average half-life of 37 hr.

Clinical and Laboratory Manifestations. In children, methadone and buprenorphine ingestions can manifest with the classic opioid toxidrome of respiratory depression, sedation, and miosis. Signs of more-severe toxicity can include bradycardia, hypotension, and hypothermia. Even in therapeutic use, methadone is associated with a prolonged QTc interval and risk of torsades de pointes. Accordingly, an ECG should be part of the initial evaluation after ingestion of methadone or any unknown opioid. Neither drug is detected on routine urine opiate screens, although some centers have added a separate urine methadone screen. Levels of both drugs can be measured, although this is rarely done clinically and is seldom helpful in the acute setting. An exception may be in the cases involving concerns about neglect or abuse, at which point urine for gas chromatography/mass spectroscopy, the legal gold standard, should be sent to confirm and document the presence of the drug.

Treatment. Patients with significant respiratory depression or CNS depression should be treated with the opioid antidote, naloxone (see Table 63-7). In pediatric patients who are not chronically on opioids, the full reversal dose of 0.1 mg/kg (max: 2 mg/dose) should be used. In contrast, opioid-dependent patients should be treated with smaller initial doses (0.01 mg/kg), which can then be repeated as needed to achieve the desired clinical response, hopefully avoiding abrupt induction of withdrawal. Because the half-lives of methadone and buprenorphine are far longer than that of naloxone, patients can require multiple doses of naloxone. These patients may benefit from a continuous infusion of naloxone, typically started at two-thirds of the reversal dose/hr and titrated to maintain an adequate respiratory rate and level of consciousness. Patients who have ingested methadone should be placed on a cardiac monitor and have serial ECGs to monitor for the development of a prolonged QTc interval. If a patient does develop a prolonged QTc, management includes close cardiac monitoring, repletion of electrolytes (potassium, calcium, and magnesium), and having magnesium and a defibrillator readily available should the patient develop torsades de pointes.

Given the potential for clinically significant and prolonged toxicity, any toddler who has ingested methadone, even if asymptomatic, should be admitted to the hospital for at least 24 hr of monitoring. Some experts advocate a similar approach to management of buprenorphine ingestions, even in the asymptomatic patient. As we gain more experience with pediatric buprenorphine exposures, some patients who remain absolutely asymptomatic for 6-8 hr after ingestion and have a stable social setting may be candidates for earlier discharge. In the meantime, these cases should be discussed with a poison control center or medical toxicologist before determining disposition.

Cardiovascular Medications

β-Adrenergic Receptor Blockers. β Blockers competitively inhibit the action of catecholamines at the β receptor. Therapeutically, β blockers are used for a variety of conditions, including hypertension, coronary artery disease, tachyarrhythmias, anxiety disorders, migraines, essential tremor, and hyperthyroidism. Because of its lipophilicity and blockade of fast sodium channels, propranolol is considered to be the most toxic member of the β-blocker class. Overdoses of water-soluble β blockers (e.g., atenolol) are associated with milder symptoms.

Pathophysiology. In overdose, β blockers decrease chronotropy and inotropy in addition to slowing conduction through atrioventricular nodal tissue. Clinically, these effects are manifested as bradycardia, hypotension, and heart block. Patients with reactive airways disease can experience bronchospasm as a result of blockade of β2-mediated bronchodilation. β Blocks interfere with glycogenolysis and gluconeogenesis, which can sometimes lead to hypoglycemia, especially in patients with poor glycogen stores (e.g., toddlers).

Clinical and Laboratory Manifestations. Toxicity typically develops within 6 hr of ingestion, although it may be delayed after ingestion of sotalol or sustained-release preparations. The most common features of severe poisoning are bradycardia and hypotension. Lipophilic agents, including propranolol, can enter the CNS and cause altered mental status, coma, and seizures. Overdose of β blockers with membrane-stabilizing properties (e.g., propranolol) can cause QRS interval widening and ventricular dysrhythmias.

Evaluation after β-blocker overdose should include an ECG, frequent reassessments of hemodynamic status, and blood glucose. Serum levels of β blockers are not readily available for routine clinical use and are not useful in management of the poisoned patient.

Treatment. In addition to supportive care and GI decontamination as indicated, glucagon is the antidote of choice for β-blocker toxicity (see Table 63-7). Glucagon stimulates adenyl cyclase and increases levels of cyclic adenosine monophosphate independent of the β receptor. Glucagon is typically given as a bolus and, if this is effective, followed by a continuous infusion. In practice, however, glucagon is often only marginally effective, limited by its prooxygenetic effects, especially at the doses typically required. Other potentially useful interventions include calcium, vasopressors, and high-dose insulin. Seizures are managed with benzodiazepines, and QRS widening should be treated with sodium bicarbonate. Children who ingest 1 or 2 water-soluble β blockers are unlikely to develop toxicity and can typically be discharged to home if they remain asymptomatic over a 6-hr observation period. Children who ingest sustained-release products, highly lipid-soluble agents, and sotalol can require longer periods of observation before safe discharge. Any symptomatic child should be admitted for ongoing monitoring and directed therapy.

Calcium Channel Blockers. Calcium channel blockers (CCBs) are used for a variety of therapeutic indications and have the potential to cause severe toxicity, even after exploratory ingestions. Specific agents include verapamil, diltiazem, and the dihydropyridines (e.g., amlodipine, nifedipine). Of these, diltiazem and verapamil are the most dangerous in overdose.

Pathophysiology. CCBs antagonize L-type calcium channels, inhibiting calcium influx into myocardial and vascular smooth muscle cells. Verapamil works primarily by slowing inotropy and chronotropy, and it has no effect on systemic vascular resistance (SVR). Diltiazem has effects both on the heart and the peripheral vasculature. The dihydropyridines exclusively diminish SVR. Verapamil and diltiazem can significantly diminish myocardial contractility and conduction, with diltiazem also lowering SVR. By contrast, dihydropyridines will drop the SVR, leading to vasodilatation and reflex tachycardia (though this receptor selectivity may be lost after a large overdose). Because the same L-type calcium channels blocked by CCBs are also on the pancreatic islet cells, it is the norm for any patient significantly poisoned with a CCB to be hyperglycemic.

Clinical and Laboratory Manifestations. The onset of symptoms typically is soon after ingestion, although it may be delayed with ingestions of sustained-release products. Overdoses of CCBs lead
to hypotension, accompanied by bradycardia, normal heart rate, or even tachycardia, depending on the agent. One unique characteristic of CCB overdose is that patients can exhibit profound hypotension with preserved consciousness.

Initial evaluation should include an ECG, continuous and careful hemodynamic monitoring, and rapid measurement of serum glucose levels. Both the absolute degree of hyperglycemia and the percentage increase in serum glucose have been correlated with the severity of CCB toxicity in adults. The development of hyperglycemia can even preclude the development of hemodynamic instability. Blood levels of CCBs are not readily available and are not useful in guiding therapy.

Treatment. Once initial supportive care has been instituted, GI decontamination should begin with activated charcoal as appropriate. WBI may be beneficial in a stable patient after ingestion of a sustained-release product. Calcium channel blockade in the smooth muscles of the GI tract can lead to greatly diminished motility; thus, any form of GI decontamination should be undertaken with careful attention to serial abdominal exams.

Calcium salts, administered either through a peripheral IV as calcium gluconate, or via a central line as calcium chloride, help to overcome blocked calcium channels. High-dose insulin euglycemia therapy is considered the antidote of choice for CCB toxicity. An initial bolus of 1 unit/kg of regular insulin is followed by an infusion at 0.5-1 unit/kg/hr (see Table 63-6). The main mechanism of high-dose insulin euglycemia is to improve the metabolic efficiency of a poisoned heart that is in need of carbohydrates for energy (instead of the usual free fatty acids), but has minimal circulating insulin. Blood glucose levels should be closely monitored, and supplemental glucose may be given to maintain euglycemia, although this is rarely necessary in the severely poisoned patient. Additional therapies include judicious IV fluid boluses and vasopressors (often in very high doses). Cardiac pacing is rarely of value, owing to the small quantities ingested and the rapid discontinuation of the drug, or even missing 1 or 2 doses, could lead to potentially dangerous elevations in blood pressure.

Digoxin. Digoxin is a cardiac glycoside extracted from the leaves of Digitalis lanata. Other natural sources of cardiac glycosides include Digitalis purpurea (foxglove), Nerium oleander (oleander), Convallaria majalis (lily of the valley), Siberian ginseng, and the Bufo marinus toad. Therapeutically, digoxin is used in the management of heart failure and some supraventricular tachydysrhythmias. Acute overdose can occur in the setting of dosing errors (especially in younger children), unintentional or intentional medication ingestion, or exposure to plant material containing digitalis glycosides. Regarding exposure to such plants, toxicity is unusual unless the poison is concentrated in the form of a tea. Chronic toxicity can result from alteration of the digoxin dose, alteration in digoxin clearance as a result of renal impairment, or drug interactions.

Pathophysiology. Digoxin blocks the Na+, K+-ATPase (adenosine triphosphatase) pump, leading to intracellular loss of K+ and gain of Na+ and Ca++. This resulting rise in Ca++ available to the contractile myocardium improves inotropy. An increase in myocardial automaticity leads to subsequent atrial, nodal, and ventricular ectopy. Digoxin also affects nodal conduction, leading to a prolonged refractory period, decreased sinus node firing, and slowed conduction through the atrioventricular node. Impaired Na-K exchange results in dangerously high levels of serum potassium. Overall, digoxin overdose manifests as a combination of slowed or blocked conduction and increased ectopy.

Clinical and Laboratory Manifestations. Nausea and vomiting are common initial symptoms of acute digoxin toxicity, manifesting within 6 hr of overdose. Cardiovascular manifestations include bradycardia, heart block, and a wide variety of dysrhythmias. CNS manifestations consist of lethargy, confusion, and weakness. Chronic toxicity is more insidious and manifests with GI symptoms, altered mental status, and visual disturbances.

Initial assessment should include an ECG, serum digoxin level, serum potassium, and kidney function tests. The serum digoxin level should be assessed at least 6 hr after ingestion and carefully interpreted in the setting of clinical symptoms because the digoxin level alone does not entirely reflect the severity of intoxication. In acute ingestions, serum potassium is less useful as a prognostic marker and may be altered due to concomitant use of diuretics.

Digoxin has a very narrow therapeutic index. Therapeutic plasma digoxin concentrations are 0.5-2.0 ng/mL; a level >2 ng/mL is considered toxic and a level >6 ng/mL is considered potentially fatal (in chronic poisonings). Numerous drug interactions affect plasma digoxin concentrations. Medications known to increase serum digoxin concentrations include the macrolides, erythromycin and clarithromycin, spironolactone, verapamil, amiodarone, and itraconazole.

Treatment. Initial treatment includes good general supportive care and gastric decontamination with activated charcoal if the ingestion was recent. An antidote for digoxin, digoxin-specific Fab antibody fragments (Digibind or DigiFab) is available (see Table 63-7). Fab fragments bind free digoxin in both the intravascular and the interstitial spaces to form a pharmacologically inactive complex that is subsequently renally eliminated. Indications for Fab fragments include life-threatening dysrhythmias, K+ value >5-5.5 mEq/L, serum digoxin level >15 ng/mL at any time or >10 ng/mL 6 hr after ingestion, ingestion >4 mg in children or >10 mg in adults, clinically significant hypotension or other cardiovascular instability, altered mental status, and renal failure. Atropine is potentially useful in managing symptomatic bradycardia. Although digoxin has severe hyperkalemia and QRS widening on the ECG, it should not receive calcium salts, this has not been supported in the literature. Once
stabilized, consultation with a cardiologist is recommended in the management of patients chronically on digoxin, because administration of Fab fragments can lead to recurrence of the patient’s underlying dysrhythmias or dysfunction.

Iron. Historically, iron was a common cause of childhood poisoning deaths. However, preventive measures such as childproof packaging have significantly decreased the rates of serious iron toxicity in young children. Iron-containing products remain widely available, with the most potentially toxic being adult iron preparations and prenatal vitamins. The severity of an exposure is related to the amount of elemental iron ingested. Ferrous sulfate contains 20% elemental iron, ferrous gluconate 12%, and ferrous fumarate 33%. Multivitamin preparations and children’s vitamins rarely contain enough elemental iron to cause significant toxicity.

Pathophysiology. Iron is directly corrosive to the GI mucosa, leading to hematemesis, melena, ulceration, infarction, and potential perforation. Early iron-induced hypotension is caused by massive volume losses, increased permeability of capillary membranes, and venodilation mediated by free iron. Iron accumulates in tissues, including the Kupffer cells of the liver and myocardial cells, leading to hepatotoxicity, coagulopathy, and cardiac dysfunction. Metabolic acidosis develops in the setting of hypotension, hypovolemia, and iron’s direct interference with oxidative phosphorylation and the Krebs cycle. Pediatric patients who ingest >40 mg/kg of elemental iron should be referred to medical care for evaluation, although moderate to severe toxicity is typically seen with ingestions of >60 mg/kg.

Clinical and Laboratory Manifestations. Iron toxicity is classically described in 4, often overlapping, stages. The initial stage, 30 min to 6 hr after ingestion, consists of profuse vomiting and diarrhea (often bloody), abdominal pain, and significant volume losses leading to potential hypovolemic shock. Patients who do not develop GI symptoms within 6 hr of ingestion are unlikely to develop serious toxicity. The 2nd stage, 6–24 hr after ingestion, is often referred to as the “quiescent phase,” as GI symptoms typically have resolved. However, careful clinical exam can reveal subtle signs of hypoperfusion, including tachycardia, pallor, and fatigue. During the 3rd stage, occurring 12–36 hr after ingestion, patients develop multisystem organ failure, shock, hepatic and cardiac dysfunction, acute lung injury or acute respiratory distress syndrome (ARDS), and profound metabolic acidosis. Death occurs most commonly during this stage. In patients who survive, the 4th stage (4–6 wk after ingestion) is marked by formation of strictures and signs of GI obstruction.

Symptomatic patients and patients with a large exposure by history should have serum iron levels drawn 4-6 hr after ingestion. Serum iron concentrations of <500 µg/dL 4-8 hr after ingestion suggest a low risk of significant toxicity, whereas concentrations of >500 µg/dL indicate that significant toxicity is likely. Additional lab evaluation in the ill patient should include arterial blood gas, complete blood count, serum glucose level, liver function tests, and coagulation parameters. Careful attention should be paid to ongoing monitoring of the patient’s hemodynamic status. An abdominal x-ray might reveal the presence of iron tablets, though not all formulations of iron are radiopaque.

Treatment. Close clinical monitoring, combined with aggressive supportive and symptomatic care, is essential to the management of iron poisoning. Activated charcoal does not adsorb iron, and WBC remains the decontamination strategy of choice. Deferoxamine, a specific chelator of iron, is the antidote for moderate to severe iron intoxication (see Table 63-7). Indications for deferoxamine treatment include a serum iron concentration of >500 µg/dL or moderate to severe symptoms of toxicity, regardless of serum iron concentration. Deferoxamine is preferably given via continuous IV infusion at a rate of 15 mg/kg/hr. Hypotension is a common side effect of deferoxamine infusion and is managed by slowing the rate of the infusion and administering fluids and/or vasopressors as needed. Prolonged deferoxamine infusion (>24 hr) has been associated with pulmonary toxicity (ARDS) and Yersinia sepsis. The deferoxamine–iron complex can color the urine reddish (“vin rose”), although this is an unreliable indicator of iron excretion. Clear end points for deferoxamine chelation are not well defined, but therapy is typically continued until clinical symptoms resolve. Consultation with a poison control center or medical toxicologist can yield guidelines for discontinuing deferoxamine.

Oral Hypoglycemics
Oral medications used in the management of type 2 diabetes include sulfonylureas, biguanides (e.g., metformin), thiazolidinediones, and meglitinides. Of these, only the sulfonylureas and meglitinides have the potential to cause profound hypoglycemia in both diabetic and nondiabetic patients. These classes of medications are widely prescribed and thus readily available for both unintentional and intentional exposures. In toddlers, ingestion of a single sulfonylurea tablet can lead to significant toxicity.

Pathophysiology. Sulfonylureas work primarily by enhancing endogenous insulin secretion. In binding to the sulfonylurea receptor, these drugs induce closure of potassium channels, leading to membrane depolarization, opening of calcium channels, and stimulation of calcium-mediated insulin release. Even in therapeutic use, the duration of hypoglycemic action can last up to 24 hr.

Clinical and Laboratory Manifestations. Hypoglycemia and symptoms associated with hypoglycemia are the primary clinical manifestations of sulfonylurea toxicity. These signs and symptoms can include diaphoresis, tachycardia, lethargy, irritability, coma, seizures, and even focal neurologic findings. As with other hyperinsulinemic states, sulfonylurea overdoses are associated with a nonketotic hypoglycemia. In the majority of cases, hypoglycemia develops within 6 hr of ingestion but can be delayed up to 16–18 hr after ingestion. Toddlers are particularly susceptible to hypoglycemia during an overnight fast.

Treatment. Patients with symptomatic hypoglycemia should be promptly treated with dextrose. In patients with mild symptoms, oral dextrose may be sufficient. However, patients with severe symptoms or profound hypoglycemia should be treated with a bolus of IV dextrose. Continuous dextrose infusions and repeated IV dextrose boluses should be avoided if possible, because this can stimulate further insulin release and lead to recurrent and prolonged hypoglycemia. Instead, the preferred antidote for symptomatic sulfonylurea toxicity is octreotide (see Table 63-7). Octreotide is a somatostatin analog that works via inhibiting insulin release. Octreotide is given IV or SC, typically in doses of 1-2 µg/kg (50-100 µg in adults) every 6-8 hr.

Given the potential for significant hypoglycemia, toddlers with witnessed or suspected sulfonylurea ingestions should be admitted to the hospital for monitoring and serial glucose measurements, at least for 12 hr, including an overnight fast. Patients of any age who develop hypoglycemia are also candidates for admission given the prolonged duration of hypoglycemic activity. Prophylactic IV dextrose infusions are not recommended because they can mask the symptoms of toxicity and stimulate further insulin secretion. Patients who require IV dextrose and/or octreotide should be monitored until they can demonstrate euglycemia for at least 8 hr off of all therapy.

With the increasing numbers of adolescents with type 2 diabetes, pediatricians should be familiar with the toxic effects of metformin as well. Although this agent does not cause hypoglycemia, its association with lactic acidosis is well documented (Metformin Associated Lactic Acidosis–MALA). This state typically arises after a large overdose in which the agent interferes with the liver’s ability to clear lactic acid. Dangerously high serum lactate levels can result, leading to hemodynamic instability. Hemodialysis is usually the best option for patients with severe metformin-associated lactic acidosis.

Psychiatric Medications: Antidepressants
Selective serotonin reuptake inhibitors (SSRIs; e.g., fluoxetine, sertraline, paroxetine, citalopram) are the most commonly prescribed class of antidepressants. This trend results in large part from their wide therapeutic index and more favorable side-effect profile when compared to older agents such as tricyclic antidepressants (TCAs; amitriptyline, clomipramine, desipramine, doxepin, nortriptyline, imipramine) and monoamine oxidase inhibitors. Other agents include the serotonin and norepinephrine reuptake inhibitors (e.g., venlafaxine) and other atypical antidepressants (e.g., bupropion).
Tricyclic Antidepressants. Although TCAs are now prescribed less commonly for depression, they remain in use for a variety of other conditions, including chronic pain syndromes, enuresis, attention-deficit/hyperactivity disorder, and obsessive compulsive disorder. TCAs can cause significant toxicity in children, even with ingestion of 1 or 2 pills (10-20 mg/kg).

Pathophysiology. TCAs achieve their desired antidepressant effects primarily via blockade of norepinephrine and serotonin reuptake. TCAs have complex interactions with other receptor types. Antagonism at muscarinic acetylcholine receptors leads to clinical features of the anticholinergic toxidrome. Antagonism at peripheral α-receptors leads to hypotension and syncope. Key to the toxicity of TCAs is their ability to block fast sodium channels, leading to impaired cardiac conduction and arrhythmias.

Clinical and Laboratory Manifestations. Cardiovascular and CNS symptoms dominate the clinical presentation of TCA toxicity. Symptoms typically develop within 1-2 hr of ingestion, and serious toxicity usually manifests within 6 hr of ingestion. Patients can have an extremely rapid progression from mild symptoms to life-threatening dysrhythmias. Patients often develop features of the anticholinergic toxidrome, including delirium, mydriasis, dry mucous membranes, tachycardia, hyperthermia, urinary retention, and slow GI motility. CNS toxicity can include lethargy, coma, myoclonic jerks, and seizures. Sinus tachycardia is the most common cardiovascular manifestation of toxicity; however, patients can develop widening of the QRS complex, premature ventricular contractions, and ventricular arrhythmias. Refractory hypotension is a poor prognostic indicator and is the most common cause of death in TCA overdose.

Treatment. Initial attention should be directed to supporting vital functions, including airway and ventilation support as needed. Gastric decontamination can be accomplished with activated charcoal in appropriate patients. Treating clinicians should obtain an ECG as soon as possible and follow serial ECGs to monitor for progression of toxicity.

Four primary effects seen at the bedside, along with their treatment recommendations, are listed here:

1. **Altered mental status.** TCA-poisoned patients can become deeply comatose relatively quickly, so careful and prompt attention to the airway and placement of an endotracheal tube is of paramount importance. The airway should be secured prior to any GI decontamination efforts.

2. **Widened QRS on the ECG.** TCAs (along with other agents such as diphenhydramine, cocaine, etc) will block the fast sodium channels on the myocardial cells, slowing the upstroke of the QRS complex. Because the effect on sodium channels is greatest within the 1st 6 hr, frequent ECGs (i.e., every 20-30 min) during this time frame are important. As the QRS approaches 160 msec, the chance of the patient developing monomorphic ventricular tachycardia rises to 30%. Sodium, usually in the form of sodium bicarbonate, is the antidote of choice. **Indications for sodium bicarbonate include a QRS duration ≥110 msec, ventricular dysrhythmias, and hypotension.** Multiple bolus doses of sodium bicarbonate, 1-2 mEq/kg each, may be needed to narrow the QRS to <110 msec. Some authors prefer to then place the patient on an infusion of sodium bicarbonate, but this may not be necessary if careful attention is paid to the QRS after the initial doses and repeat bolus dosing is provided as needed during those 1st 6-12 hr. Hypertonic (3%) saline and/or lipid emulsion therapy may be beneficial in refractory cases.

3. **Hypotension.** A direct acting vasopressor, such as norepinephrine or epinephrine, is the agent of choice. Boluses of intravenous crystalloid fluids should be used with caution to prevent fluid overload.

4. **Seizures.** Likely a result of the anticholinergic effects of TCAs, seizures are relatively common, typically brief, and should be treated with agents the work on the γ-aminobutyric acid receptor complex in the brain. Benzodiazepines are the agent of choice. Asymptomatic children should receive appropriate decontamination and be observed with continuous cardiac monitoring and serial ECGs for at least 6 hr. If any manifestations of toxicity develop, the child should be admitted to a monitored setting. Children who remain completely asymptomatic with normal serial ECGs may be candidates for discharge after 6 hr of close observation.

**Selective Serotonin Reuptake Inhibitors.** In overdose, SSRIs are considerably less toxic than TCAs. SSRIs are unlikely to cause significant toxicity in exploratory ingestions. Some data suggest that initiating SSRI therapy is associated with an increased risk of suicidal ideation and behavior (see Chapter 21).

Pathophysiology. SSRIs selectively block the reuptake of serotonin in the CNS. In contrast to TCAs and atypical antidepressants, SSRIs do not directly interact with other receptor types.

Clinical and Laboratory Manifestations. In overdose, the principal manifestations of toxicity are sedation and tachycardia. Cardiac conduction abnormalities (primarily QTc prolongation) and seizures have been described in significant overdoses, especially after ingestions of citalopram. An ECG should be part of the initial assessment after SSRI ingestion. Serum creatine kinase levels are almost always elevated in a patient with clinically significant serotonin syndrome. Although development of the serotonin syndrome is seen more often after therapeutic use or overdose of several serotonergic agents in combination, it has also been described in ingestions of SSRIs alone (Table 63-11). Clinically, serotonin syndrome describes a spectrum of altered mental status, autonomic instability, fever, and neuromuscular hyperactivity (hyperreflexia, tremors, clonus in the lower extremities more than the upper extremities). One or all of these signs may be present to varying degrees.

Treatment. Initial management includes a careful assessment for signs and symptoms of serotonin syndrome and an ECG. Most patients simply require supportive care and observation until their mental status improves and tachycardia, if present, resolves. Management of serotonin syndrome is directed by the severity of symptoms; possible therapeutic interventions include benzodiazepines in mild cases and intubation, sedation, and paralysis in patients with severe manifestations (e.g., significant hyperthermia). Because agonism at the 5-HT_{1A} serotonin receptor is thought to be primarily responsible for the development of serotonin syndrome, use of the 5HT_{1A} receptor antagonist cyproheptadine is also beneficial. Cyproheptadine is only available in an oral form.

Atypical Antidepressants. The class known as atypical antidepressants includes agents such as venlafaxine and duloxetine (serotonin and norepinephrine reuptake inhibitors), bupropion (dopamine, norepinephrine, and some serotonin reuptake blockade), and...
trazodone (serotonin reuptake blockade and peripheral α-receptor antagonism). The variable receptor affinities of these agents lead to some distinctions in their clinical manifestations and management. Clinical and Laboratory Manifestations. In overdose, venlafaxine and other serotonin and norepinephrine reuptake inhibitors are associated with cardiac conduction defects, including QRS and QTc prolongation, and seizures. Bupropion is one of the most common causes of cardiac toxicity in the pediatric population. Antipsychotic medications are commonly classified as either typical or atypical. In general, typical agents are associated with more side effects and toxicity than the atypical agents. Pathophysiology. Typical or traditional antipsychotics (i.e., haloperidol, droperidol, thioridazine, chlorpromazine, and fluphenazine) are characterized by their antagonism at D2 dopamine receptors. In therapeutic use, these agents are associated with extrapyramidal symptoms, tardive dyskinesia, and development of the neuroleptic malignant syndrome (NMS). The atypical agents (i.e., aripiprazole, clozapine, quetiapine, risperidone, ziprasidone) were developed with less dopamine (D2-receptor) antagonism in efforts to avoid these side effects and improve their efficacy in managing the “negative” symptoms of schizophrenia. Instead, these agents have complex and varied interactions with multiple receptor types, including α-receptors, serotonin receptors, muscarinic acetylcholine receptors, and histamine receptors. Clinical and Laboratory Manifestations. Typical antipsychotic toxicity commonly includes sedation, tachycardia, and prolongation of the QTc interval. Patients can present with acute dystonia, akathisia, and NMS, although these are seen less commonly in acute overdoses than in therapeutic use. The phenothiazines (e.g., thioridazine) can cause widening of the QRS interval owing to blockade of fast sodium channels. Clinically, NMS can be difficult to distinguish from serotonin syndrome. Although the presentation of atypical antipsychotic toxicity can vary based on the receptor affinities of the specific agent, sedation, tachycardia, and QTc prolongation are common. Peripheral α-receptor blockade (e.g., with quetiapine) is associated with hypotension. In therapeutic use, clozapine is associated with agranulocytosis. Diagnostic testing should include an ECG. Patients with hyperthermia or muscle rigidity should have a serum creatine kinase level sent to monitor for possible rhabdomyolysis. Antipsychotic levels are not readily available and are not helpful in managing acute poisoning. Management. Initial management involves assessing and supporting vital functions. In some patients, CNS depression may be so profound as to require intubation for airway control. Acute dystonia is treated with diphenhydramine, benztropine, and sometimes benzodiazepines. Management of NMS includes conscientious supportive care, IV fluids, cooling, benzodiazepines, and bromocriptine or dantrolene in severe cases. QTc prolongation is managed with repletion of electrolytes (especially calcium, magnesium, and potassium), continuous cardiac monitoring, overdrive pacing, IV magnesium sulfate and/or defibrillation if the patient develops torsades de pointes. Seizures typically are well controlled with benzodiazepines. Hypotension usually responds to boluses of IV fluids, though vasopressor therapy is necessary in some cases. Household Products Caustics Caustics include acids and alkalis as well as a few common oxidizing agents (see Chapter 327). Strong acids and alkalis can produce severe injury even in small-volume ingestions. Pathophysiology. Alkalis produce a liquefaction necrosis, allowing further tissue penetration of the toxin and setting the stage for possible perforation. Acids produce a coagulative necrosis, which limits further tissue penetration, though perforation can still occur. The severity of the corrosive injury depends on the pH and...
concentration of the product as well as the length of contact time with the product. Agents with a pH of <2 or >12 are most likely to produce significant injury.

**Clinical Manifestations.** Ingestion of caustic materials can produce injury to the oral mucosa, esophagus, and stomach. Patients can have significant esophageal injury even in the absence of visible oral burns. Symptoms include pain, drooling, vomiting, abdominal pain, and difficulty swallowing or refusal to swallow. Laryngeal injury can manifest as stridor and respiratory distress, necessitating intubation. In the most severe cases, patients can present in shock after perforation of a hollow viscus. Circumferential burns of the esophagus are likely to cause strictures when they heal, which can require repeated dilation or surgical correction and long-term follow-up for neoplastic changes in adulthood (see Chapter 327.2). Caustics on the skin or in the eye can cause significant tissue damage.

**Treatment.** Initial treatment of caustic exposures includes thorough removal of the product from the skin or eye by flushing with water. Emesis and lavage are contraindicated. Activated charcoal should not be used because it does not bind these agents and can predispose the patient to vomiting and subsequent aspiration. Stridor or other signs of respiratory distress should alert the provider to the need for a thorough evaluation of the airway for potential intubation or surgical airway management. Endoscopy can be performed within 12-24 hr of ingestion for prognostic and diagnostic purposes in symptomatic patients or those in whom injury is suspected on the basis of history and known characteristics of the ingested product. Endoscopy is contraindicated in any patient with signs of perforation. The use of corticosteroids or prophylactic antibiotics is not beneficial.

**Cholinesterase-Inhibiting Insecticides**

The most commonly used insecticides are organophosphates and carbamates; both are inhibitors of cholinesterase enzymes (acetylcholinesterase, pseudocholinesterase, and erythrocyte acetylcholinesterase). Most pediatric poisonings occur as the result of unintentional exposure to insecticides in and around the home or farm. The class of chemical warfare weapons known as “nerve agents” are also organophosphate compounds with a similar mechanism of action, but much greater potency.

**Pathophysiology.** Organophosphates and carbamates produce toxicity by binding to and inhibiting acetylcholinesterase, preventing the degradation of acetylcholine and resulting in its accumulation at nerve synapses. If left untreated, organophosphates form an irreversible bond to acetylcholinesterase, permanently inactivating the enzyme. This process, called aging, occurs over a variable time period depending on the characteristics of the specific organophosphate. Afterwards, a period of weeks to months is required to regenerate inactivated enzymes. In contrast, carbamates form a temporary bond to the enzymes, typically allowing reactivation of acetylcholinesterase within 24 hr.

**Clinical and Laboratory Manifestations.** Clinical manifestations of organophosphate and carbamate toxicity relate to the accumulation of acetylcholine at peripheral nicotinic and muscarinic synapses and in the CNS. Symptoms of carbamate toxicity are usually less severe than those seen with organophosphates. A commonly used mnemonic for the symptoms of cholinergic excess at muscarinic receptors is **DUMBELLS**, which stands for diarrhea/defecation, urination, miosis, bronchorrhia/bronchospasm, bradycardia, emesis, lacrimation, and salivation. Nicotinic signs and symptoms include muscle weakness, fasciculation, tremors, hypoventilation (diaphragm weakness), hypertension, tachycardia, and dysrhythmias. Severe manifestations include coma, seizures, shock, arrhythmias, and respiratory failure.

Diagnosis of poisoning is based primarily on history and physical exam findings. Red blood cell cholinesterase and pseudocholinesterase activity levels can be measured in the laboratory. These are only helpful if the patient’s known baseline. As such, these assessments are typically limited to farm workers undergoing ongoing occupational surveillance.

**Treatment.** Basic decontamination should be performed, including washing all exposed skin with soap and water and immediately removing all exposed clothing. Activated charcoal is unlikely to be of benefit as these are liquids that are rapidly absorbed. Basic supportive care should be provided, including fluid and electrolyte replacement and intubation and ventilation if necessary. The use of succinylcholine for rapid sequence intubation should be avoided as this paralytic is metabolized by the same cholinesterase enzymes now poisoned, leading to prolonged paralysis.

Two antidotes are useful in treating cholinesterase inhibitor poisoning: atropine and pralidoxime (see Table 63-7). Atropine, which antagonizes the muscarinic acetylcholine receptor, is useful for both organophosphate and carbamate intoxication. Often, large doses of atropine must be administered by intermittent bolus or via continuous infusion to control symptoms. Atropine dosing is primarily targeted to drying the respiratory secretions. Pralidoxime breaks the bond between the organophosphate and the enzyme, reactivating acetylcholinesterase. Pralidoxime is only effective if it is used before the bond ages and becomes permanent. Pralidoxime is not necessary for carbamate poisonings because the bond between the insecticide and the enzyme degrades spontaneously.

Without treatment, symptoms of organophosphate poisoning can persist for weeks, requiring continuous supportive care. Even with treatment, some patients develop a delayed polyneuropathy and a range of chronic neuropsychiatric symptoms.

**Hydrocarbons**

Hydrocarbons include a wide array of chemical substances found in thousands of commercial products. Specific characteristics of each product determine whether exposure will produce systemic toxicity, local toxicity, both, or neither. Nevertheless, aspiration of even small amounts of certain hydrocarbons can lead to serious, potentially life-threatening toxicity.

**Pathophysiology.** The most important manifestation of hydrocarbon toxicity is aspiration pneumonitis via inactivation of the type II pneumocytes and resulting surfactant deficiency (see Chapter 397). Aspiration usually occurs during coughing and gagging at the time of ingestion or vomiting after the attempted ingestion of an ali-phatic hydrocarbon. The propensity of a hydrocarbon to cause aspiration pneumonitis is inversely proportional to its viscosity, and directly proportional to its volatility. Compounds with low viscosity and high volatility, such as mineral spirits, naphtha, kerosene, gasoline, and lamp oil, spread rapidly across surfaces and cover large areas of the lungs when aspirated. Only small quantities (<1 mL) of such chemicals need be aspirated to produce significant injury. Pneumonitis does not result from dermal absorption of hydrocarbons or from ingestion in the absence of aspiration. Gasoline and kerosene are poorly absorbed, but they often cause considerable irritation of the GI mucosa as they pass through the intestines.

Certain hydrocarbons have unique toxicities and can cause symptoms after ingestion, inhalation, or dermal exposures. Several chlorinated solvents, most notably carbon tetrachloride, can produce hepatic toxicity. Methylene chloride, found in some paint removers, is metabolized to carbon monoxide. Benzene is known to cause cancer, most commonly acute myelogenous leukemia, after long-term exposure. Nitrobenzene, aniline, and related compounds can produce methemoglobinemia. A number of volatile hydrocarbons, including toluene, propellants, refrigerants, and volatile nitrites, are commonly abused by inhalation. Some of these substances, principally the halogenated hydrocarbons (which contain a chlorine, bromine, or fluorine), can sensitize the myocardium to the effects of endogenous catecholamines. This can result in dysrhythmias and “sudden sniffing death.” Chronic abuse of these agents can lead to cerebral atrophy, neuropsychologic changes, peripheral neuropathy, and kidney disease (see Chapter 114).

**Clinical and Laboratory Manifestations.** Transient, mild CNS depression is common after hydrocarbon ingestion or inhalation. Aspiration is characterized by coughing, which usually is the first clinical finding. Chest radiographs may initially be normal, but they often show abnormalities within 6 hr of exposure in patients who have aspirated. Respiratory symptoms can remain mild or progress rapidly to ARDS and respiratory failure. Fever and leukocytosis are common accompanying signs in patients with pneumonitis and don’t necessarily
Early symptoms onset of serious effects, including profound metabolic acidosis and measured by the freezing point depression method and compared with gap does not rule out ingestion of any alcohol. Serum osmolality is usually difficult based on history. Methanol blood levels are available an anion gap metabolic acidosis as the parent compound is metabolized, noted. Initially, patients have an elevated osmolar gap and then develop acidosis is well established. These visual defects may be reversible if treated early, but untreated they can lead to permanent blindness. On acidosis is delayed up to 4-12 hr after ethylene glycol ingestion, and may be delayed further with any concomitant ingestion of ethanol. Ethylene glycol blood concentrations are technically difficult to perform and are available only at some larger reference laboratories. In the absence of readily available ethylene glycol concentrations, calculation of the osmolar gap may be helpful as a surrogate marker.

Examination of the urine with a Wood lamp is neither sensitive nor specific for ethylene glycol ingestion. The earliest sign on a urinalysis of ethylene glycol poisoning is usually hematuria. Calcium oxalate crystals can be seen on urine microscopy but might not be evident early after exposure. Electrolytes (including calcium), acid–base status, kidney function, and ECG should be closely monitored in poisoned patients.

Treatment. Because methanol and ethylene glycol are rapidly absorbed, gastric decontamination is generally not of value. The classic antidote for methanol and ethylene glycol poisoning was ethanol, a preferential substrate for alcohol dehydrogenase, thus preventing the metabolism of parent compounds to toxic metabolites. Fomepizole (see Table 63-7), a potent competitive inhibitor of alcohol dehydrogenase, has almost entirely replaced the use of ethanol owing to its ease of administration, lack of CNS and metabolic effects, and overall excellent patient tolerability profile. As with all poisons, a serum concentration must be interpreted along with the time removed from exposure. A patient with a methanol level of 20 mg/dL 24 hr after exposure had a much larger dose than a patient with the same level only 1 hr after ingestion. Indications for fomepizole include ethylene glycol or methanol level >20 mg/dL, history of potentially toxic ingestion (e.g., any intentional overdose), or history of ingestion with evidence of acidosis. There are few disadvantages to giving the initial dose of fomepizole to patients with a concerning history of ingestion or lab findings, and given the dosing schedule of fomepizole (every 12 hr), this strategy buys the clinician time to confirm or exclude the diagnosis before giving a second dose. Adjunctive therapy includes folate (methanol toxicity), pyridoxine (ethylene glycol toxicity) and sodium bicarbonate infusions for both (if acidic). If a child has had an unintentional exposure and a level of the alcohol cannot be obtained, a reasonable approach is to follow serum chemistries every 4 hr until the child is 12 hr removed from the exposure. If the bicarbonate level on the chemistry panel does not fall in that time frame, then a toxic exposure is unlikely (assuming no ethanol is present).

Hemodialysis effectively removes ethylene glycol, methanol, and their metabolites (except calcium oxalate) and corrects acid–base and electrolyte disturbances. Fomepizole should be given both before and immediately after dialysis. Indications for dialysis include a methanol level of >50 mg/dL, acidosis, severe electrolyte disturbances, and renal failure. However, in the absence of acidosis and kidney failure, even massive ethylene glycol ingestions have been managed without dialysis. Methanol is another story, because its elimination in the setting of alcohol dehydrogenase inhibition is very prolonged, thus often warranting dialysis to remove the parent compound. Therapy (fomepizole and/or dialysis) should be continued until ethylene glycol and methanol levels are <20 mg/dL. While the visual effects from

Toxic Alcohols Methyl alcohol is commonly found in windshield washer fluids, deicers, paint removers, fuel additives, liquid fuel canisters, and industrial solvents. Ethylene glycol is commonly found in antifreeze. Unintentional ingestion is the most common exposure in children, and small-volume ingestions of concentrated products can theoretically cause toxicity. The pathophysiology, acid–base derangements, and treatment of both chemicals are similar, although they differ in their primary end-organ toxicity. In both cases, the metabolites of the parent compounds are responsible for the serious clinical effects that can follow exposure.

Isopropyl alcohol (rubbing alcohol, hand sanitizers) causes intoxication similar to that associated with ethanol but can also cause a hemorrhagic gastritis and myocardial depression in massive ingestions. Unlike ethylene glycol and methanol, isopropyl alcohol is metabolized to a ketone and does not cause a metabolic acidosis. Management is similar to that of ethanol ingestions (see Chapter 114) and is not further discussed here.

Methanol Pathophysiology. Methanol is oxidized in the liver by alcohol dehydrogenase to formaldehyde, which is further oxidized to formic acid by aldehyde dehydrogenase. Toxicity is caused primarily by formic acid, which inhibits mitochondrial respiration.

Clinical and Laboratory Manifestations. Drowsiness, mild inebriation, nausea, and vomiting develop early after ingestion. The onset of serious effects, including profound metabolic acidosis and visual disturbances, is often delayed for up to 12-24 hr as the parent methanol is undergoing metabolism to its toxic metabolites. This metabolism is further slowed if ethanol has also been ingested, since the liver will preferentially metabolize ethanol. Visual disturbances include blurred or cloudy vision, constricted visual fields, decreased acuity, and the “feeling of being in a snowstorm” appear only after acidosis is well established. These visual defects may be reversible if treated early, but untreated they can lead to permanent blindness. On exam, dilated pupils, retinal edema, and optic disc hyperemia may be noted. Initially, patients have an elevated osmolar gap and then develop an anion gap metabolic acidosis as the parent compound is metabolized to formic acid.

In young children, determining if a significant exposure has occurred is usually difficult based on history. Methanol blood levels are available at some laboratories and should be sent after a concerning exposure. If methanol blood levels are not readily available, estimation of an osmolar gap may be used as a surrogate marker, but a normal osmolar gap does not rule out ingestion of any alcohol. Serum osmolality is measured by the freezing point depression method and compared with a calculated serum osmolarity.

Treatment. Treatment is as discussed for ethylene glycol toxicity.
methanol poisoning are usually permanent, the kidney injury from ethylene glycol injury is not. Patients requiring hemodialysis after ethylene glycol poisoning will almost always recover complete renal function within 2-6 wk. Consultation with a poison control center, medical toxicologist, and nephrologist may be helpful in managing toxic alcohol ingestions.

**Plants**

Exposure to plants, both inside the home and outside in backyards and fields, is one of the most common causes of unintentional poisoning in children. Fortunately, the majority of ingestions of plant parts (leaves, seeds, flowers) result in either no toxicity or mild, self-limiting effects. However, ingestion of certain plants (Table 63-12 outlines some of the most toxic plants) can lead to serious toxicity.

The potential toxicity of a particular plant is highly variable, depending on the part of the plant involved (flowers are generally less toxic than the root or seed), the time of year, growing conditions, and the route of exposure. Assessment of the potential severity after an exposure is also complicated by the difficulty in properly identifying the plant. Many plants are known by several common names, which can vary among communities. Poison control centers have access to professionals who can assist in properly identifying plants. They also are well versed in the common poisonous plants in their service area and the seasons when they are more abundant. For these reasons, consultation with the local poison control center may be very helpful in the management of these ingestions.

For potentially toxic plant ingestions, consider decontamination with activated charcoal in patients who present within 1-2 hr of ingestion; otherwise, treatment is primarily supportive and based on symptoms. The most common manifestation of toxicity after plant ingestion is GI upset, which can be managed with antiemetics and fluid and electrolyte support. Table 63-12 outlines management strategies for a few specific toxicities.

**Toxic Gases**

**Carbon Monoxide**

Although many industrial and naturally occurring gases pose a health risk by inhalation, the most common gas involved in pediatric exposures is carbon monoxide (CO). CO is a colorless, odorless gas produced during the combustion of any carbon-containing fuel. The less efficient the combustion, the greater the amount of CO produced. Wood-burning stoves, kerosene heaters, old furnaces or hot water heaters and automobiles are a few of the potential sources of CO, as is any closed space fire.

**Pathophysiology.** CO binds to hemoglobin with an affinity >200 times that of oxygen, forming carboxyhemoglobin (HbCO). In doing so, CO displaces oxygen and creates a conformational change in hemoglobin that impairs the delivery of oxygen to the tissues, leading to tissue hypoxia. HbCO levels are not well correlated with clinical signs of toxicity, likely because CO interacts with multiple proteins in addition to hemoglobin. CO binds to cytochrome oxidase, disrupting cellular respiration. CO displaces nitric oxide (NO) from proteins, allowing NO to bind with free radicals to form the toxic metabolite peroxynitrite. NO is also a potent vasodilator, in part responsible for clinical symptoms including headache, syncope, and hypotension.

**Clinical and Laboratory Manifestations.** Early symptoms are nonspecific and include headache, malaise, nausea, and vomiting. These symptoms are often misdiagnosed as indicating flu or food poisoning. At higher exposure levels, patients can develop mental status changes, confusion, ataxia, syncope, tachycardia, and tachypnea. Severe poisoning is manifested by coma, seizures, myocardial ischemia, acidosis, cardiovascular collapse, and potentially death. On exam, patients might have cherry-red skin. Emergency department evaluation should include an arterial or venous blood gas with HbCO determined by co-oximetry, and lactate assays. Severe poisoning, defined as a HbCO level >25%, abnormal cerebellar examination, and pregnancy. Consultation with a poison control center, medical toxicologist, or HBO facility can assist clinicians in determining which patients could benefit from HBO therapy. Sequelea of CO poisoning include persistent and delayed cognitive and cerebellar effects. HBO advocates believe that the risk of such sequelae is minimized through the delivery of 100% oxygen at 3 atmospheres of pressure. Patients are typically treated with oxygen, via either non-rebreather or a hyperbaric chamber, for between 6 and 24 hr. Prevention of CO poisoning should involve educational initiatives and the use of home CO detectors.

**Hydrogen Cyanide**

**Pathophysiology.** Cyanide inhibits cytochrome oxidase, part of the electron transport chain, interrupting cellular respiration and leading to profound tissue hypoxia. Patients may be exposed to hydrogen cyanide gas in the workplace (manufacturing of synthetic fibers, nitriles, and plastics) or via smoke inhalation in a fire.

**Clinical and Laboratory Manifestations.** Onset of symptoms is rapid after a significant exposure. Clinical manifestations of toxicity include headache, agitation and confusion, sudden loss of consciousness, tachycardia, cardiac dysrhythmias, and metabolic acidosis. Cyanide levels can be measured in whole blood, but they are not readily available at most institutions. A severe lactic acidosis (lactate >10 mmol/L) in fire victims suggests cyanide toxicity. Impaired oxygen extraction by tissues is implied by elevated mixed venous oxygen saturation, another laboratory finding suggesting cyanide toxicity.

**Treatment.** Treatment includes removal from the source of exposure, rapid administration of high concentrations of oxygen, and antidotal therapy. The cyanide antidote kit includes nitrates (amyl nitrite and sodium nitrite) used to produce methemoglobin, which then reacts with cyanide to form cyanomethemoglobin (see Table 63-7). The third part of the kit is sodium thiosulfate, given to hasten the metabolism of cyanomethemoglobin to hemoglobin and the less-toxic thiocyanate. In patients for whom induction of methemoglobinemia could produce more risk than benefit, the sodium thiosulfate component of the kit may be given alone. The FDA has approved hydroxocobalamin (a form of vitamin B12) for use in known or suspected cyanide poisoning. This antidote reacts with cyanide to form the nontoxic cyanocobalamin, which is then excreted in urine. Side effects of hydroxocobalamin include red discoloration of the skin and urine, transient hypertension, and interference with colorimetric lab assays. Overall, the safety profile of hydroxocobalamin appears superior to that of the cyanide antidote kit; thus this is now the preferred antidote for cyanide poisoning.

**Some Miscellaneous Toxic Agents Found in the Home**

**Single-Use Detergent Sacs**

Commonly known as laundry “pods” for clothing, these products look like candy to many children. When bitten into, a relatively large dose of concentrated detergent is expelled under pressure onto the child’s posterior pharynx and vocal cords. This can lead to stridor and other signs of respiratory distress. Occasionally, and for unknown reasons, these children may also develop altered mental status. Supportive care with attention to any airway and breathing issues is warranted. Admission to the hospital is often indicated. It should be noted, that these are not considered caustic ingestions. The pH of these products is in the neutral zone. As such, upper GI endoscopy is rarely indicated. Curiously, laundry detergent drank from a bottle is rarely of significant concern.
Chapter 63  •  Poisoning

## Batteries

Any disk or button style battery lodged in the esophagus or airway should be considered a true emergency warranting immediate referral to an endoscopist for removal. These batteries can cause necrosis of the tissues to which they are lodged via continued electrical discharge and/or leaking of their contents (the former is likely the primary method of injury). Mucosal contact for even 2 hr might induce necrosis. Once past the lower esophageal sphincter, button or even larger batteries (e.g., AA, AAA size) can usually be allowed to pass through the GI tract with close follow up.

**Bibliography is available at Expert Consult.**

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### Table 63-12  Commonly Ingested Plants with Significant Toxic Potential

<table>
<thead>
<tr>
<th>PLANT</th>
<th>SYMPTOMS</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autumn crocus (Colchicum autumnale)</td>
<td>Vomiting, Diarrhea, Initial leukocytosis followed by bone marrow failure, Multisystem organ failure</td>
<td>Activated charcoal decontamination, Aggressive fluid resuscitation and supportive care</td>
</tr>
<tr>
<td>Belladonna alkaloids: jimson weed (Datura stramonium) Belladonna (“deadly nightshade”; Atropa belladonna)</td>
<td>Anticholinergic toxidrome, Seizures</td>
<td>Supportive care, benzodiazepines, Consider physostigmine if patient is a threat to self or others; only use if no conduction delays on ECG</td>
</tr>
<tr>
<td>Cardiac glycoside–containing plants (foxglove, lily of the valley, oleander, yellow oleander, etc)</td>
<td>Nausea, Vomiting, Bradycardia, Dysrhythmias (AV block, ventricular ectopy), Hyperkalemia</td>
<td>Digoxin-specific Fab fragments</td>
</tr>
<tr>
<td>Jequirity bean and other abrin-containing species (e.g., rosary pea, precatory bean)</td>
<td>Oral pain, Vomiting, Diarrhea, Shock, Hemolysis, Renal failure</td>
<td>Supportive care, including aggressive volume resuscitation and correction of electrolyte abnormalities</td>
</tr>
<tr>
<td>Monkshood (Aconitum species)</td>
<td>Numbness and tingling of lips/tongue, Vomiting, Bradycardia</td>
<td>Atropine for bradycardia, Supportive care</td>
</tr>
<tr>
<td>Oxalate-containing plants: Philodendron, Dieffenbachia, Colocasia (“elephant ear”)</td>
<td>Local tissue injury, Oral pain, Vomiting</td>
<td>Supportive care, pain control</td>
</tr>
<tr>
<td>Poison hemlock (Conium maculatum)</td>
<td>Vomiting, Agitation followed by CNS depression, Paralysis, Respiratory failure</td>
<td>Supportive care</td>
</tr>
<tr>
<td>Pokeweed</td>
<td>Hemorrhagic gastroenteritis, Burning of mouth and throat</td>
<td>Supportive care</td>
</tr>
<tr>
<td>Rhododendron</td>
<td>Vomiting, Diarrhea, Bradycardia</td>
<td>Atropine for symptomatic bradycardia, Supportive care</td>
</tr>
<tr>
<td>Tobacco</td>
<td>Vomiting, Agitation, Diaphoresis, Fasciculations, Seizures</td>
<td>Supportive care</td>
</tr>
<tr>
<td>Water hemlock (Cicuta species)</td>
<td>Abdominal pain, Vomiting, Delirium, Seizures</td>
<td>Supportive care, including benzodiazepines for seizures</td>
</tr>
<tr>
<td>Yew (Taxus species)</td>
<td>GI symptoms, QRS widening, Hypotension, CV collapse</td>
<td>Supportive care, Atropine for bradycardia, Sodium bicarbonate does not appear to be effective</td>
</tr>
</tbody>
</table>

AV, atrioventricular; CNS, central nervous system; CV, cardiovascular; ECG, electrocardiogram; Fab, fragment, antigen binding; GI, gastrointestinal.

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**Electric Dishwasher Detergent**

Especially when in the form of crystals, these products are highly alkaline (pH >13) and exposure via ingestion can lead to significant burns to the vocal cords and GI tract. Admission for upper GI endoscopy is usually indicated.

**Magnets**

Most foreign body ingestions are allowed to pass through the GI tract once they are known to have passed into the stomach. However, ingestion of 2 or more magnets (unless they are very weak refrigerator style magnets) cause concern for bowel obstruction and/or perforation. Admission for attempted retrieval via endoscopy or clearance via WBI is to be considered.
Complementary Therapies and Integrative Medicine
Kathi J. Kemper and Paula M. Gardiner

Integrative medicine focuses on promoting physical, mental, emotional, spiritual, social, educational, and occupational well-being in the context of a medical home in a healthy family and community. The foundations of integrative medicine are health-promoting practices including optimal nutrition and dietary supplements to avoid deficiencies; avoiding intake of addictive substances such as nicotine and illicit drugs; physical activity, adequate sleep, a healthy environment, and supportive social relationships. Evidence-based complementary therapies such as herbal remedies and other dietary supplements, massage, chiropractic, and other forms of bodywork, yoga, tai chi, meditation practices, hypnosis, guided imagery, biofeedback, and acupuncture may also be used. Although prayer and healing rituals are sometimes included under the rubric of complementary and integrative therapies, they are not covered in this chapter.

Not including multivitamins and mineral supplements (such as iron and calcium), the estimated prevalence of complementary and alternative medicine use in the United States by youth younger than 18 yr of age in 2007 was 8.7 million; the most common therapies included natural products, chiropractic, and deep breathing. Use of complementary therapies is most common among youth with chronic, incurable, or recurrent conditions such as asthma, autism, cancer, depression, and pain. For example, complementary therapies were used by 42-71% of pediatric patients in a 2013 study of specialty outpatient clinics in Canada; the therapies most commonly used by these patients were dietary supplements. Side effects were uncommon and most were minor.

**Dietary Supplements**

Under the 1994 Dietary Supplement Health and Education Act, a dietary supplement is a product taken by mouth that contains a dietary ingredient intended to supplement the diet. These may include vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites. Dietary supplements are the most commonly used complementary therapies for children and adolescents (Table 64-1). Some uses are common and recommended, such as vitamin D supplements for breastfed infants and probiotics to prevent *Clostridium difficile*-associated diarrhea, whereas other uses are more controversial, such as using herbal products to treat otitis media.

In the United States, dietary supplements do not undergo the same stringent evaluation and postmarketing surveillance as prescription medications. Although they may not claim to prevent or treat specific medical conditions, product labels may make structure-function claims. For example, a label may claim that a product promotes a healthy immune system, but it may not claim to cure the common cold.

According to the 2007 National Health Interview Survey, 37% of children in the United States used dietary supplements, with the majority using multivitamin and mineral products (31%) exclusively. Use of dietary supplements is most common among children whose families have higher income and education and whose parents use them; among older children; and among those suffering from chronic conditions.

Despite this widespread use, many patients and their parents who use dietary supplements do not talk with their physician about their use. Several guidelines have called for more complete dietary supplement history taking by healthcare professionals. The Joint Commission recommends that clinicians routinely ask patients about their use of dietary supplements and include this information as part of the medication reconciliation process.

**Dietary Supplement Safety**

Dietary supplements may have safety issues in children, though toxicity is much less common with nonprescription dietary supplements than with prescription medications. Toxicity depends on dose, use of other medications, and the underlying medical condition of the child. Modern use of a dietary supplement (e.g., ephedra for weight loss) may not reflect its traditional use (e.g., ephedra as a component of a traditional Chinese medicine tea in small doses to improve allergic or respiratory symptoms). Moreover, herbs that are apparently safe for most adults may be more hazardous in specific conditions (e.g., newborns, patients with impaired renal or hepatic function), under special circumstances (e.g., after organ transplantation or other surgery), or when combined with prescription medications. Some natural products are toxic in and of themselves (Table 64-2). Acute hepatic toxicity and death can result from ingestion of even small amounts of *Amanita* mushrooms. Even when a product is safe when used correctly, it can cause mild or severe toxicity when used incorrectly. Although peppermint is a commonly used and usually benign gastrointestinal spasmylytic included in after-dinner mints, it can exacerbate gastroesophageal reflux. Probiotics are generally safe when taken orally, but in an immune-compromised patient in an ICU setting, they may (rarely) cause sepsis.

### Table 64-1 Most Commonly Used Dietary Supplements in Pediatrics

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>USES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VITAMINS</strong></td>
<td></td>
</tr>
<tr>
<td>B1 (riboflavin)</td>
<td>Migraine headache prophylaxis</td>
</tr>
<tr>
<td>B6 (pyridoxine)</td>
<td>Pyridoxine-dependent epilepsy; neuropathy; nausea associated with pregnancy</td>
</tr>
<tr>
<td>B9 (folate)</td>
<td>Prevention of neural tube defects</td>
</tr>
<tr>
<td>D</td>
<td>Prevention of rickets; treatment of deficiencies</td>
</tr>
<tr>
<td>Multivitamins</td>
<td>General health promotion, ADHD</td>
</tr>
<tr>
<td><strong>MINERALS</strong></td>
<td></td>
</tr>
<tr>
<td>Iodine (salt)</td>
<td>Prevent goiter and mental retardation</td>
</tr>
<tr>
<td>Iron</td>
<td>Prevent and treat iron deficiency</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Constipation, asthma, migraine prevention</td>
</tr>
<tr>
<td>Zinc</td>
<td>Diarrhea in nutrient-poor populations</td>
</tr>
<tr>
<td><strong>HERBS</strong></td>
<td></td>
</tr>
<tr>
<td>Aloe vera</td>
<td>Mild burns</td>
</tr>
<tr>
<td>Chamomile</td>
<td>Mild sedative, dyspepsia</td>
</tr>
<tr>
<td>Echinacea</td>
<td>Prevention of upper respiratory infections</td>
</tr>
<tr>
<td>Ginger</td>
<td>Nausea</td>
</tr>
<tr>
<td>Lavender (aromatherapy)</td>
<td>Mild sedative</td>
</tr>
<tr>
<td>Peppermint</td>
<td>Irritable bowel syndrome</td>
</tr>
<tr>
<td>Tea tree oil</td>
<td>Anti-bacterial (acne remedies), pediculicide (lice)</td>
</tr>
<tr>
<td><strong>OTHER</strong></td>
<td></td>
</tr>
<tr>
<td>Melatonin</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Omega-3 fatty acids (fish oil)</td>
<td>ADHD, allergies, inflammation, anxiety and mood disorders</td>
</tr>
<tr>
<td>Probiotics</td>
<td>Antibiotic-associated diarrhea; <em>Clostridium difficile</em>-associated diarrhea; constipation; irritable bowel syndrome; pouchitis; inflammatory bowel disorders</td>
</tr>
</tbody>
</table>

ADHD, attention-deficit/hyperactivity disorder.
<table>
<thead>
<tr>
<th>HERB</th>
<th>TOXIC CONSTITUENTS</th>
<th>TYPICAL USES</th>
<th>POTENTIAL ACUTE ADVERSE EFFECTS</th>
<th>HOW TO TREAT OVERDOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aconitum (monkshood, wolfsbane)</td>
<td>Diester alkaloids: Hypaconitine and aconitine (aconitine increases permeability for sodium ions and slows down repolarization, leading to paralysis of the nerve)</td>
<td>Facial neuralgia and sciatica Headache and migraines Rheumatic pain, arthritis, gout Pericarditis sicca</td>
<td>Nausea, vomiting, hypersalivation CNS: Paresthesias, muscular weakness, dizziness, ataxia, seizures, coma Cardiac: Bradycardia, hypotension, rhythm disorders</td>
<td>Supportive care Dioxin-specific antibodies, unless history excludes cardiac glycosides Do not give ipecac Activated charcoal and gastric emptying might help Avoid type 1 antiarrhythmics</td>
</tr>
<tr>
<td>Artemisia absinthium (wormwood)</td>
<td>Thujone and isothujone: Neurotoxins</td>
<td>Anorexia Dyspeptic conditions Liver and gallbladder disorders</td>
<td>Mental status changes: Restlessness, vertigo, tremors, agitation, seizures, headache Vomiting; stomach and intestinal cramps Rhabdomyolysis and renal failure</td>
<td>Supportive care Benzodiazepines</td>
</tr>
<tr>
<td>Atropa belladonna (deadly nightshade) of atropine</td>
<td>Alkaloids: Hyoscyamine (the L-isomer)</td>
<td>Gastrointestinal symptoms Cardiac insufficiency and arrhythmia Asthma</td>
<td>Anticholinergic reaction: Tachycardia, hyperthermia, mydriasis, urine and feces retention, restlessness Nervous system and respiratory depression</td>
<td>Gastric lavage Physostigmine given in consultation with a poison specialist External cooling if temperature is &gt;38.9°C (102°F) Benzodiazepines Hydration</td>
</tr>
<tr>
<td>Ayurvedic herbal remedies</td>
<td>Contaminated with lead, mercury, or arsenic</td>
<td>Traditional medicine from India; many purposes</td>
<td>Acute or chronic heavy metal toxicity</td>
<td>Depends on heavy metal</td>
</tr>
<tr>
<td>Digitalis purpurea (foxglove)</td>
<td>Cardioactive glycosides: Purpurea glycoside, digitoxin</td>
<td>Ulcers, boils, headaches, abscesses, paralysis, cardiac insufficiency</td>
<td>Nausea and vomiting, headache, loss of appetite Cardiac rhythm disorders CNS: Stupor, confusion, visual disorders, depression, psychosis, hallucinations</td>
<td>Supportive care Gastric lavage Activated charcoal Treatment of symptoms</td>
</tr>
<tr>
<td>Ephedra sinica (ma huang) Common names: Miner's tea, Mexican tea, Desert herb</td>
<td>Alkaloids: Ephedrine, pseudoephedrine (stimulates sympathomimetic receptors and the CNS)</td>
<td>Decongestant for upper respiratory infection Asthma Weight loss Stimulant</td>
<td>Cardiac: Hypertension, cardiomyopathy, myocardial infarction, arrhythmias CNS: Dizziness, restlessness, headaches, anxiety, hallucinations, tremors, seizures, psychosis, strokes Nausea and vomiting Contraindicated in diabetes or hypertension, angle-closure glaucoma, anxiety, prostate adenoma, thyroid disease, pheochromocytoma</td>
<td>Activated charcoal Benzodiazepine for seizures and sedation Vasodilators for hypertension Lidocaine and β blockers for arrhythmias External cooling if temperature is &gt;38.9°C (102°F) Hydration therapy</td>
</tr>
<tr>
<td>Illicium anisatum (Japanese star anise tea)</td>
<td>Anisatins; block γ-aminobutyric acid</td>
<td>Colic in Latino and Caribbean populations</td>
<td>Seizures, tonic postures, myoclonus, hyperexcitability, irritability</td>
<td>Recovery with supportive care within 48 hr</td>
</tr>
<tr>
<td>Lobelia inflata (lobelia)</td>
<td>Piperidine alkaloid: L-Lobeline (stimulates nicotinic receptors)</td>
<td>Expectorant Asthma Spasmolytic Emetic To induce mental clarity and a feeling of well-being</td>
<td>Gastrointestinal: Nausea and vomiting, abdominal pain, diarrhea CNS: Anxiety, headache, dizziness, tremors, seizures, paresthesias, euphoria Cardiac: Arrhythmias, bradycardia, transient increase in blood pressure, decreased respiratory rate In overdose, lobeline can cause hypotension Diaphoresis, muscle fasciculations and weakness, tremors, respiratory depression Dermatitis</td>
<td>Supportive care Gastric emptying Activated charcoal Benzodiazepines</td>
</tr>
</tbody>
</table>
Although there are good manufacturing practices for dietary supplements in the United States, dietary supplement labels might not accurately reflect the contents or concentrations of ingredients. Because of natural variability, variations of 10-1,000-fold have been reported for many popular herbs, even across lots produced by the same manufacturer. Herbal products may be unintentionally contaminated with pesticides, microbial agents or products, or the wrong herb that was misidentified during harvesting. Products from developing countries may be unintentionally contaminated with mercury, cadmium, arsenic, or lead, either from unintentional contamination during manufacturing or from intentional additions by producers who believe that these metals have therapeutic value. Approximately 30-40% of Asian patent medicines include potent pharmaceuticals, such as analgesics, antibiotics, hypoglycemic agents, or corticosteroids; typically, the labels for these products are not written in English and do not note the inclusion of pharmaceutical agents. Even conventional mineral supplements, such as calcium, have been contaminated with lead or had significant problems with product variability.

Many families use supplements concurrently with medications, posing hazards of interactions (Table 64-3). St. John’s wort induces CYP3A4 activity of the P450 enzyme system and thus can enhance elimination of most drugs, including digoxin, cyclosporine, protease inhibitors, oral contraceptives, and numerous antibiotics, leading to...
<table>
<thead>
<tr>
<th>HDS</th>
<th>DRUGS</th>
<th>POTENTIAL CONSEQUENCES/REACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Hydroxytryptophan</td>
<td>Fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine</td>
<td>↑Risk of serotonin syndrome</td>
</tr>
<tr>
<td>Acacia</td>
<td>Amoxicillin</td>
<td>↓Absorption of amoxicillin</td>
</tr>
<tr>
<td>Alfalfa</td>
<td>Warfarin</td>
<td>↓The effect of warfarin</td>
</tr>
<tr>
<td>Aloe vera</td>
<td>Digoxin</td>
<td>↑Digoxin toxicity</td>
</tr>
<tr>
<td>American ginseng</td>
<td>Warfarin</td>
<td>↓The effect of warfarin</td>
</tr>
<tr>
<td>Arginine</td>
<td>Enalapril, nitroglycerin, Spironolactone</td>
<td>↑Hypotensive effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑Risk of hyperkalemia</td>
</tr>
<tr>
<td>Bitter orange</td>
<td>Phenelzine</td>
<td></td>
</tr>
<tr>
<td>Cowhage</td>
<td>Methyldopa</td>
<td>↑Risk of hypertensive crisis</td>
</tr>
<tr>
<td>Danshen</td>
<td>Aspirin, ticlopidine, warfarin</td>
<td>↑Risk of bleeding</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
<td>↑Digoxin toxicity</td>
</tr>
<tr>
<td>Digitalis</td>
<td>Bendroflumethiazide, chlorothiazide, chlorothalidone, hydrochlorothiazide, hydroflumethiazide, indapamide, methyclothiazide, metolazone, polythiazide, trichlormethiazide, Digoxin</td>
<td>↑Digoxin toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dong quai</td>
<td>Aspirin, heparin, ticlopidine, warfarin</td>
<td></td>
</tr>
<tr>
<td>Evening primrose</td>
<td>Warfarin</td>
<td>↑Risk of bleeding</td>
</tr>
<tr>
<td>Garlic</td>
<td>Ritonavir, Saquinavir, Warfarin</td>
<td>↓The effect of ritonavir</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓The effect of saquinavir</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑Risk of bleeding</td>
</tr>
<tr>
<td>Ginkgo</td>
<td>Aspirin, cilostazol, clopidogrel, dipyridamole, heparin, ibuprofen, naproxen, ticlopidine, warfarin</td>
<td>↑Risk of bleeding</td>
</tr>
<tr>
<td></td>
<td>Risperidone, Trazodone</td>
<td>↑Risk of risperidone adverse effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Excessive sedation and potential coma</td>
</tr>
<tr>
<td>Glucosamine</td>
<td>Warfarin</td>
<td>↑Risk of bleeding</td>
</tr>
<tr>
<td>Green tea</td>
<td>Ephedrine</td>
<td>↑Risk of stimulatory adverse effects</td>
</tr>
<tr>
<td>Guarana</td>
<td>Ephedrine</td>
<td>↑Risk of stimulatory adverse effects</td>
</tr>
<tr>
<td>Hawthorn</td>
<td>Digoxin</td>
<td>↑Digoxin toxicity</td>
</tr>
<tr>
<td>Henbane</td>
<td>Chlorpheniramine, clemastine, dimenhydrinate, diphenhydramine, doxylamine, promethazine</td>
<td>↑Risk of anticholinergic side effects</td>
</tr>
<tr>
<td>Kava</td>
<td>Alprazolam, clordiazepoxide, clonazepam, diazepam, estazolam, flurazepam, lorazepam, midazolam, morphine, oxazepam, phenobarbital, quazepam, temazepam, triazolam, Droperidol</td>
<td>↑Central nervous system depression</td>
</tr>
<tr>
<td>Licorice</td>
<td>Warfarin</td>
<td>↑Risk of bleeding</td>
</tr>
<tr>
<td>L-Tryptophan</td>
<td>Citalopram, duloxetine, fluoxetine, fluvoxamine, isocarboxazid, paroxetine, phenelzine, selegiline, sertraline, sibutramine, tranylcypromine, venlafaxine, Zolpidem</td>
<td>↑Risk of serotonin syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑Zolpidem-induced side effect</td>
</tr>
<tr>
<td>Melatonin</td>
<td>Zolpidem</td>
<td>↑Sedative effects</td>
</tr>
<tr>
<td>N-Acetylcysteine</td>
<td>Nitroglycerin</td>
<td>Severe hypotension, intolerable headaches</td>
</tr>
<tr>
<td>Niacin</td>
<td>Atorvastatin, cerivastatin, lovastatin, rosuvastatin, simvastatin</td>
<td>↑Risk of myopathy or rhabdomyolysis</td>
</tr>
<tr>
<td>PABA</td>
<td>Dapsone, Sulfamethoxazole</td>
<td>↓Antibacterial effect</td>
</tr>
<tr>
<td>Pleurisy root</td>
<td>Digoxin</td>
<td>↑Digoxin toxicity</td>
</tr>
<tr>
<td>Potassium</td>
<td>Amlodine, benazepril, captopril, enalapril, fosinopril, indomethacin, lisinopril, moexipril, quinapril, ramipril, spironolactone, trandolapril, triamterene</td>
<td>↑Risk of hyperkalemia</td>
</tr>
<tr>
<td>Red yeast rice</td>
<td>Cyclosporine</td>
<td>↑Creatine phosphokinase values</td>
</tr>
<tr>
<td>S-Adenosylmethionine</td>
<td>Clomipramine</td>
<td>↑Risk of serotonin syndrome</td>
</tr>
<tr>
<td>Scotch broom</td>
<td>Haloperidol, Phenelzine</td>
<td>↑The potential toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑Risk of hypertensive crisis</td>
</tr>
<tr>
<td>Valerian</td>
<td>Alprazolam, phenobarbital</td>
<td>↑Central nervous system depression</td>
</tr>
</tbody>
</table>

Continued
Table 64-3 | The HDS–Drug Interactions with Major Severity* (Other Than St. John’s Wort—cont’d

<table>
<thead>
<tr>
<th>HDS</th>
<th>DRUGS</th>
<th>POTENTIAL CONSEQUENCES/REACTIONS†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>Acitretin, bexarotene, etretinate, isotretinoin, tretinoin</td>
<td>↑Risk of vitamin A toxicity</td>
</tr>
<tr>
<td>Vitamin B₆</td>
<td>Altretamine</td>
<td>↓Response to altretamine</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Dicumarol</td>
<td>↑Risk of bleeding</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>Warfarin</td>
<td>↓Effect of warfarin</td>
</tr>
<tr>
<td>Willow</td>
<td>Diclofenac, ibuprofen, naproxen, ticlopidine, warfarin</td>
<td>↑Risk of bleeding</td>
</tr>
</tbody>
</table>

*Any HDS–drug interactions with severity rated as contraindicated or major in either database of MicroMedex or NMCD were included in this table.
†Potential consequences or reactions were documented according to either aforementioned database with severity rating as major or contraindicated.
↑, increasing; ↓, decreasing; HDS, herb and dietary supplements; PABA, para-aminobenzoic acid.


Table 64-4 | Common Folk Medicines By Cultural Origin

<table>
<thead>
<tr>
<th>NAME</th>
<th>CONTENTS</th>
<th>POTENTIAL TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>HISPANIC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Siete jarabes</td>
<td>Almond, castor oil, tolu, wild cherry licorice, cocillana, honey</td>
<td>GI upset, catharsis, electrolyte disturbances</td>
</tr>
<tr>
<td>Agua maravilla</td>
<td>Witch hazel, ethanol</td>
<td>Ethanol toxicity</td>
</tr>
<tr>
<td>Jarabe maguey</td>
<td>Maguey (Agave spp)</td>
<td>GI upset, catharsis, electrolyte disturbances</td>
</tr>
<tr>
<td>Alcanfor</td>
<td>Camphor</td>
<td>Camphor toxicity</td>
</tr>
<tr>
<td>Azarcon</td>
<td>Lead</td>
<td>Lead intoxication</td>
</tr>
<tr>
<td>Greta</td>
<td>Lead</td>
<td>Lead intoxication</td>
</tr>
<tr>
<td>Azogue</td>
<td>Elemental mercury</td>
<td>Mercury intoxication</td>
</tr>
<tr>
<td>Ipecacuana</td>
<td>Ipecac</td>
<td>Vomiting, myopathy</td>
</tr>
<tr>
<td>SOUTHEAST ASIAN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paylooah</td>
<td>Lead</td>
<td>Lead intoxication</td>
</tr>
<tr>
<td>INDIAN AND AYURVEDIC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surma</td>
<td>Lead</td>
<td>Lead intoxication</td>
</tr>
<tr>
<td>Deshi Dawa</td>
<td>Lead</td>
<td>Lead intoxication</td>
</tr>
</tbody>
</table>

GI, gastrointestinal.


Subtherapeutic serum levels. In contrast, St. John’s wort may enhance the risk of the serotonin syndrome in patients on selective serotonin reuptake inhibitor agents, increase the sedation of opioids, increase the photosensitivity reactions of certain drugs, and increase the toxicity of propofol and sevoflurane.

Many folk medicine are named based on their natural language (Tables 64-4 and 64-5), which must be taken into consideration when treating specific ethnic populations.

Dietary supplement efficacy
Evidence about the effectiveness of dietary supplements to prevent or treat pediatric problems is mixed, depending on the product used and condition treated. Some herbal products may be helpful adjunctive treatments for common childhood problems; some herbs have proved helpful for colic (fennel and the combination of chamomile, fennel, vervain, licorice, and balm mint), nausea (ginger), irritable bowel syndrome (peppermint), and diarrhea (probiotics).

Massage and chiropractic
Massage is commonly provided at home by parents and by professional massage therapists, physical therapists, and nurses in clinical settings. Infant massage is routinely provided in many neonatal intensive care units to promote growth and development in preterm infants. Massage also has been demonstrated to be beneficial for pediatric patients suffering from asthma, insomnia, colic, cystic fibrosis, and juvenile ideopathic arthritis. Massage therapy is generally safe. Professional massage practice is regulated by state governments; more than 40 states license massage therapists, and 3 offer statewide independent certification.

More than 50,000 chiropractors are licensed in the United States, including licensure in all 50 states. Chiropractic care is covered by most major insurers. Up to 14% of all chiropractic visits are for pediatric patients, not including care provided by chiropractors working for athletic departments or professional teams. While chiropractic care may be useful for treating minor musculoskeletal injuries, parents need to be cautioned not to rely on chiropractic as the primary treatment for serious conditions, such as neurologic deficits, cancer or autism; data suggest that severe complications are possible.

Mind–body therapies
Mind–body therapies such as slow, deep breathing, meditation, guided imagery, biofeedback, hypnosis, tai chi, and yoga, are the second most commonly used group of complementary therapies in pediatrics. These practices can be learned informally through books, YouTube videos, CDs, DVDs, smart phone applications, or classes, or in therapeutic sessions with health professionals, such as psychologists and social workers (Table 64-6). Substantial research suggests that such practices can aid in reducing anxiety, insomnia, and stress-related conditions including migraine headaches and functional abdominal pain. They can also help patients struggling with chronic pain.
Table 64-5  Spanish-English Botanical Name Translation Chart

<table>
<thead>
<tr>
<th>SPANISH NAME</th>
<th>ENGLISH NAME</th>
<th>BOTANICAL NAME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ajo</td>
<td>Garlic</td>
<td>Allium sativum</td>
</tr>
<tr>
<td>Cebolla</td>
<td>Onion</td>
<td>Allium cepa</td>
</tr>
<tr>
<td>Cenela</td>
<td>Cinnamon</td>
<td>Cinnamomum aromaticum</td>
</tr>
<tr>
<td>Clavo</td>
<td>Cloves</td>
<td>Eugenia aromatica</td>
</tr>
<tr>
<td>Comino</td>
<td>Cumin</td>
<td>Cuminum cyminum</td>
</tr>
<tr>
<td>Epasote or herba Sancti Mariae</td>
<td>Wormseed</td>
<td>Chenopodium anhalminticum</td>
</tr>
<tr>
<td>Estafiate</td>
<td>Wormwood</td>
<td>Artemisia absinthium</td>
</tr>
<tr>
<td>Eucalipto</td>
<td>Eucalyptus</td>
<td>Eucalyptus globulus</td>
</tr>
<tr>
<td>Granada</td>
<td>Pomegranate</td>
<td>Punica granatum</td>
</tr>
<tr>
<td>Jengibre</td>
<td>Ginger</td>
<td>Zingiber officinale</td>
</tr>
<tr>
<td>Limon</td>
<td>Lemon</td>
<td>Citrus limon</td>
</tr>
<tr>
<td>Manzanilla</td>
<td>Chamomile</td>
<td>Anthemis nobilis or Chamomilla recutita or Matricaria chamomilla</td>
</tr>
<tr>
<td>Oregano</td>
<td>Oregano</td>
<td>Origanum vulgare</td>
</tr>
<tr>
<td>Pelos de elote</td>
<td>Corn silk</td>
<td>Zea mays</td>
</tr>
<tr>
<td>Savila</td>
<td>Aloe vera</td>
<td>Aloe vera</td>
</tr>
<tr>
<td>Tomillo</td>
<td>Thyme</td>
<td>Thymus vulgaris</td>
</tr>
<tr>
<td>Una de gato</td>
<td>Cat's claw</td>
<td>Uncaria tomentosa</td>
</tr>
<tr>
<td>Valeriana</td>
<td>Valerian</td>
<td>Valeriana officinalis</td>
</tr>
<tr>
<td>Yerba buena</td>
<td>Spearmint</td>
<td>Mentha spicata</td>
</tr>
</tbody>
</table>

Table 64-6  Commonly Used Mind–Body Practices in Pediatrics

<table>
<thead>
<tr>
<th>PRACTICE</th>
<th>USES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biofeedback</td>
<td>Preventing migraine headaches; reducing stress and anxiety; encopresis/constipation treatment; treatment of stress incontinence; neurofeedback is experimental for ADHD</td>
</tr>
<tr>
<td>Deep breathing</td>
<td>Relaxation; stress management</td>
</tr>
<tr>
<td>Guided imagery</td>
<td>Stress management, anxiety, pain relief</td>
</tr>
<tr>
<td>Hypnosis</td>
<td>Correcting habit disorders; preventing headaches; managing pain</td>
</tr>
<tr>
<td>Meditation</td>
<td>Stress management, improving concentration</td>
</tr>
<tr>
<td>Tai chi</td>
<td>Improved balance, coordination, concentration, discipline</td>
</tr>
<tr>
<td>Yoga</td>
<td>Improved balance, coordination, concentration</td>
</tr>
</tbody>
</table>

ACUPUNCTURE
Modern acupuncture incorporates treatment traditions from China, Japan, Korea, France, and other countries. In the United States, acupuncturists are licensed to practice in 43 states, and acupuncture services are offered by more than 30% of North American academic pediatric pain treatment programs. The technique that has undergone most scientific study involves penetrating the skin with thin, solid, metallic needles manipulated by hand or by electrical stimulation. Variants include rubbing (shiatsu), heat (moxibustion), lasers, magnets, pressure (acupressure), or electrical currents.

Although most pediatric patients are averse to needles, patients who suffer from severe chronic pain or nausea may be amenable to trying acupuncture and often report that it is helpful. Acupuncture can offer significant benefits in the treatment of recurrent headache, anxiety, back and other types of pain, depression, and nausea. As with any therapy involving needles, infections and bleeding can occur, but more serious complications, such as pneumothorax, occur in <1 in 30,000 treatments.

Bibliography is available at Expert Consult.

Internet Resources
American Academy of Pediatrics Section on Integrative Medicine: http://www2.aap.org/sections/chim/default.cfm
Consortium of Academic Health Centers for Integrative Medicine: http://www.imconsortium.org/
National Institutes of Health’s National Center for Complementary and Integrative Medicine: http://nccam.nih.gov
Natural Medicines Comprehensive Database (requires subscription): http://www.naturaldatabase.com
Natural Standard (requires subscription): http://www.naturalstandard.com
US Department of Defense Total Force Fitness: http://hprc-online.org/total-force-fitness
Bibliography


Acutely ill children pose a challenge to a busy pediatrician’s office. Illnesses can span the spectrum from simple viral infections to life-threatening emergencies. Pediatricians need to distinguish between patients who can be managed with close outpatient follow-up and those that need to be stabilized and transported to a higher level of care. Although patients of all ages can present with similar symptoms, the etiology of the illness can be age-dependent. The initial approach must focus on the general evaluation and stabilization of the acutely ill infant and child.

HISTORY

A thorough history is paramount to arriving at the correct diagnosis. Obtaining an accurate history from young patients is challenging, and parents often provide the most important information. On the basis of the chief complaint(s), the pediatrician must ask open-ended questions that help distinguish between common and potentially life-threatening entities. Common complaints leading to acute care visits for potential emergencies include fever, altered mental status, vomiting, respiratory distress, and abdominal pain.

Fever is the most common reason for a sick child visit. Most fevers are the result of self-limited viral infections. However, pediatricians need to be aware of the age-dependent potential for serious bacterial infections (e.g., urinary tract infections, sepsis, meningitis, pneumonia, dysentery, osteoarticular infection). During the first 2-3 mo of life, the neonate is at risk for sepsis caused by pathogens that are uncommon in older children. These organisms include group B streptococcus, Escherichia coli, Listeria monocytogenes, and herpes simplex virus. In neonates, the history must include maternal obstetric information and the patient’s birth history. Risk factors for sepsis include maternal group B streptococcus colonization, prematurity, chorioamnionitis, and prolonged rupture of membranes. If there is a maternal history of sexually transmitted infections during the pregnancy, the differential diagnosis must be expanded to include those pathogens. Septic infants can present with lethargy, poor feeding, grunting respirations, and cool or mottled extremities, in addition to fever (or hypothermia). Infants with fever, irritability, and a bulging fontanel should be evaluated for meningitis. As the infant matures beyond 3 mo of age, the bacterial pathogens that usually cause bacteremia, sepsis, and meningitis are Streptococcus pneumoniae, Haemophilus influenzae type b, and Neisseria meningitidis. Urosepsis secondary to an E. coli urinary tract infection also needs to be considered. Immunization against some serotypes of S. pneumoniae has markedly reduced the occurrence of occult bacteremia and serious infections caused by that organism, as has immunization against H. influenzae type b. These remain potential concerns in those children not fully immunized against these pathogens. Other ailments that manifest with fever include septic arthritis and osteomyelitis, juvenile idiopathic arthritis, and Kawasaki disease. Children with a septic joint generally present with only 1 joint that is painful and often have pseudoparalysis of that joint. In contrast, patients with juvenile rheumatoid arthritis may present with pain, stiffness, swelling, and warmth of several joints. The diagnosis of Kawasaki disease should be considered if the patient meets the diagnostic criteria for this illness although some patients may have an atypical or incomplete presentation (see Chapter 166).

For patients presenting with altered mental status, the pediatrician should inquire about the presence of other symptoms, such as fever or headache. Screening questions should be asked regarding feeding changes, medications in the household, or the possibility of trauma. Parents will often describe a febrile child as “lethargic.” but further questioning will reveal a tired-appearing child who interacts appropriately when the child has defervesced. Febrile patients need to be differentiated from the lethargic patient who presents with sepsis or meningitis. Infants with meningitis or sepsis may have a history of irritability, inconsolability, poor feeding, grunting respirations, seizures, decreased urine output, and/or color changes such as pallor, mottling, or cyanosis. Patients with poisonings or inborn errors of metabolism can also present with lethargy, poor feeding, unusual odors, seizures, and/or vomiting. Nonaccidental trauma should always be considered in a lethargic infant. Older children may present with altered mental status as a result of meningitis/encephalitis, trauma, or ingestions. Children with meningitis may have a history of fever and complaints of neck pain; other associated symptoms can include rash, headache, photophobia and/or vomiting. Children with ingestions can present with other abnormal neurologic symptoms such as ataxia, slurred speech, seizures, or characteristic constellations of vital sign changes and other physical findings (toxidromes).

Vomiting is a very common complaint of intestinal, other abdominal (e.g., pancreas, liver) or nongastrointestinal (e.g., hyperammonemia, increased intracranial pressure, poisoning) origin and may be a nonspecific sign of systemic illness. Questions to ask include about the presence of bilious or bloody emesis, abdominal distention, weight changes, presence of diarrhea, obstipation or hematochezia, history of trauma, and presence of headache. Although common causes of vomiting are gastroesophageal reflux and viral gastroenteritis, the pediatrician needs to be aware of other serious causes. In the infant, bilious emesis and abdominal distention and/or pain are worrisome for obstruction, as may be seen with malrotation with midgut volvulus or Hirschsprung disease. It is important to consider extraabdominal causes of vomiting in the neonate, including hydrocephalus, incarcerated hernia, inborn errors of metabolism, and nonaccidental trauma. Markedly increasing head circumference or a bulging fontanel can be the result of congenital hydrocephalus or can signal the presence of subdural hematomas from nonaccidental trauma. An infant who appears immediately hungry after projectile vomiting suggests a differential diagnosis of pyloric stenosis. In an older child, the differential diagnosis includes intussusception, incarcerated hernia, diabetic ketoacidosis, appendicitis, poisonings, and trauma. Patients with intussusception may present with vomiting and colicky abdominal pain. A history of increased urination in the presence of vomiting may herald the diagnosis of diabetes mellitus. Patients with headache and vomiting may present with an increased intracranial pressure and should be questioned about neurologic changes, meningismus, and fever.

Parents can interpret different symptoms as respiratory distress. Tachypnea secondary to fever is often a source of parental anxiety. Parents of newborn infants are sometimes alarmed by the presence of periodic breathing. Normal variations in respiratory patterns must be distinguished from true respiratory distress. Parents need to be questioned regarding associated symptoms such as fever, limitation of neck movement, drooling, choking, and the presence of stridor or wheezing.
A history of apnea or cyanosis warrants further investigation. Although wheezing is often secondary to bronchospasm, it can also be caused by cardiac disease or congenital anomalies such as vascular rings. Infants with congenital heart defects may be tachypneic but may lack any signs of respiratory distress as a compensatory mechanism for shock or metabolic acidosis. Parents often confuse and interpret stridor as wheezing, and care should be taken to differentiate the two. Stridor is most commonly caused by croup. However, anatomic abnormalities such as laryngeal webs, laryngomalacia, subglottic stenosis, and paralyzed vocal cords also cause stridor. Toddlers who present with wheezing or stridor after a coughing or choking episode should be evaluated for a foreign body aspiration. In toxic-appearing children with stridor, the pediatrician should consider epiglottitis, bacterial tracheitis, or a rapidly expanding retropharyngeal abscess. The incidence of epiglottitis has markedly declined with the advent of the H. influenzae type b (Hib) vaccine, but remains a possibility in the unimmunized or partially immunized patient. Children with retropharyngeal abscesses may also present with drooling and limitation of neck movement (especially hyperextension) after a recent upper respiratory infection or penetrating mouth injury.

Abdominal pain is another frequent complaint. Often this symptom is caused by a minor illness such as constipation, functional abdominal pain, urinary tract infection, or gastroenteritis. Parents should be questioned about associated symptoms including stooling patterns, abdominal distention, fever, urinary symptoms, and vomiting. In neonates, a tender abdomen is concerning for the presence of a small bowel obstruction; these infants tend to appear ill. There may be a history of vomiting and decreased or no stooling. Pediatricians should be wary of neonates with abdominal tenderness and bloody stools, as 10% of cases of necrotizing enterocolitis occur in term infants. Infants with milk protein intolerance can also present with bloody stools, but these infants are well-appearing and do not have abdominal tenderness. In older patients, the differential diagnosis for a potential emergency with abdominal pain expands to include intussusception and appendicitis. Patients with intussusception can present in a variety of ways, ranging from having episodes of colicky abdominal pain, but otherwise well in between episodes, to being lethargic or in shock. The diagnosis of appendicitis in the child younger than 3 yr is extremely difficult because children in this age group do not localize their pain well. Often the diagnosis is made after the appendix has ruptured.

The child’s past medical history also needs to be obtained. It is important to be aware of any underlying chronic problems that might predispose the child to recurring infections or a serious acute illness. The child with sickle cell anemia is at increased risk for bacteremia, as well as painful vasoocclusive crisis. A careful review of systems can help in identifying the nature of the acute illness, as well as any complications needing intervention, such as dehydration accompanying an otherwise minor viral illness.

**PHYSICAL EXAM**

Observation is important in the evaluation of the acutely ill child. Most observational data that the pediatrician gathers during an acute illness should focus on assessing the child’s response to stimuli. Do they awaken easily with a stimulus? Do they smile and interact with the examiner? Can the crying child be consoled by the parents’ comforting? Assessing responses to stimuli requires knowledge of normal responses for different age groups, the manner in which those normal responses are elicited, and to what degree a response might be impaired. Thus, the pediatrician must be both clinically and developmentally oriented.

During the physical examination, the pediatrician seeks evidence of illness. The portions of the physical examination that require the child to be most cooperative are completed first. Initially, it is best to seat the child on the parent’s lap; the older child may be seated on the examination table. It is also important to assess the child’s willingness to move and ease of movement. It is reassuring to see the child moving about on the parent’s lap with ease and without discomfort. Vital signs are often overlooked but are invaluable in assessing ill children. The degree of fever, the presence of tachycardia out of proportion to the fever, and the presence of tachypnea and hypotension all suggest a serious infection. The respiratory evaluation includes determining respiratory rate, the presence or absence of hypoxia by pulse oximetry, and noting any evidence of inspiratory stridor, expiratory wheezing, grunting, coughing, or increased work of breathing (e.g., retractions, nasal flaring, belly breathing). Because acute infections in children are most often caused by viral infections, the presence of nasal discharge may be noted. It is possible at this time to assess the skin for rashes. Frequently, viral infections cause an exanthem and many of these eruptions are diagnostic (e.g., the reticulated rash and “slapped-cheek” appearance of parvovirus infections or the typical appearance of hand-foot-and-mouth disease caused by coxsackieviruses). The skin examination may also yield evidence of more serious infections (bacterial cellulitis or petechiae and purpura associated with bacteremia). Cutaneous perfusion should be assessed by warmth and capillary refill time. When the child is seated and is least perturbed, an assessment of the fontanel can be completed; the examiner can determine whether the fontanel is depressed, flat, or bulging.

During this initial portion of the physical examination, when the child is most comfortable, the heart and lungs are auscultated. In the acutely febrile child, because of the relatively frequent occurrence of respiratory illnesses, it is important to assess adequacy of air entry into the lungs, equality of breath sounds, and evidence of adventitial breath sounds, especially wheezes, rales, and rhonchi. The coarse sound of air moving through a congested nasal passage is frequently transmitted to the lungs. The examiner can become attuned to these coarse sounds by placing the stethoscope near the child’s nose and then compensating for this sound as the chest is auscultated. The cardiac examination is next; findings such as pericardial friction rub, loud murmurs, and distant heart sounds may indicate an infectious process involving the heart. The eyes are examined to identify features that might indicate an infectious process. Often, viral infections result in a watery discharge or redness of the bulbar conjunctivae. Bacterial infection, if superficial, results in purulent drainage; if the infection is more deep-seated, tenderness, swelling, and redness of the tissues surrounding the eye are present, as well as proptosis, reduced visual acuity, and altered extraocular movement. The extremities may then be evaluated not only for ease of movement but also for the possibility of swelling, heat, or tenderness; such abnormalities may indicate focal infections.

The components of the physical examination that are more bothersome to the child are completed last. This is best done with the patient on the examination table. Initially, the neck is examined to assess for areas of swelling, redness, or tenderness, as may be seen in cervical adenitis. Resistance to neck movement should prompt evaluation for signs of meningeal irritation (i.e., Kernig and Brudzinski signs) or a retropharyngeal abscess. During examination of the abdomen, the diaphragm is removed. The abdomen is inspected for distention. Auscultation is performed to assess adequacy of bowel sounds, followed by palpation. The child often fusses as the abdomen is auscultated and palpated. Every attempt should be made to quiet the child; if this is not possible, increased fussing as the abdomen is palpated may indicate tenderness, especially if this finding is reproducible. In addition to focal tenderness, palpation may elicit involuntary guarding or rebound tenderness (including tenderness to percussion); these findings indicate peritoneal irritation, as is seen in appendicitis. The inguinal area and genitals are then sequentially examined. The child is then placed in the prone position, and abnormalities of the back are sought. The spine and costovertebral angle areas are percussed to elicit any tenderness; such a finding may be indicative of vertebral osteomyelitis or diskitis and pyelonephritis, respectively.

Examining the ears and throat completes the physical examination. These are usually the most bothersome parts of the examination for the child, and parents frequently can be helpful in minimizing head movement. During the oropharyngeal examination, it is important to document the presence of enanthemas; these may be seen in many infectious processes, such as hand-foot-and-mouth disease caused by coxsackievirus. This portion of the examination is also important in documenting inflammation or exudates on the tonsils, which may be viral or bacterial.
Repeating portions of the assessment may be indicated. If the child cried continuously during the initial clinical evaluation, the examiner may not be certain whether the crying was caused by the high fever, stranger anxiety, or pain, or is indicative of a serious or localizing illness. Constant crying also makes portions of the physical examination, such as auscultation of the chest, more difficult. Before a repeat assessment is performed, efforts to make the child as comfortable as possible are indicated.

Febrile children can appear very ill, initially appearing listless, tachycardic, and tachypneic. These patients should receive antipyretic medications and be reassessed once they have defervesced. In the majority of children with uncomplicated viral illnesses, the vital signs normalize. Persistence of abnormal vital signs should prompt the clinician to further investigate the source of fever. Continued tachycardia and poor perfusion may be secondary to myocarditis. Tachypnea may be the sole symptom in patients with pneumonia, especially in children whose chief complaint is abdominal pain due to lower lobe pneumonia. Persistent irritability suggests meningitis/encephalitis.

**RISK FACTORS**

The sensitivity of the carefully performed clinical assessment, observation, history, and physical examination for the presence of serious illness is approximately 90%. If a serious illness is suspected, other data should be sought to improve this sensitivity level. Important supplemental data are age, body temperature, and the results of screening laboratory tests as indicated. Febrile children in the first 3 mo of life have yet to achieve immunologic maturity and therefore are more susceptible to severe infections. Thus, the febrile infant is at greater risk for serious bacterial infection than the child beyond 3 mo of age and warrants careful evaluation. Data from the era before widespread immunization for *H. influenzae* type b and pneumococcus suggest the risk of bacteremia in infants increases as the magnitude of fever increases; it is unclear how this applies today.

Screening laboratory tests may be helpful in identifying the febrile child at increased risk for selected serious illnesses. Practice guidelines from the prevaccine era suggested that white blood cell count might be useful in establishing a higher risk of bacteremia. Because the incidence of occult pneumococcal bacteremia in febrile children has declined significantly as a result of the introduction of conjugated pneumococcal vaccine, the utility of white blood cell count in otherwise healthy febrile young children older than 2–3 mo of age is questionable. Urinalysis and urine culture must always be considered when the source of fever is not apparent, especially in the highest-risk groups: females and uncircumcised males younger than 2 yr of age and all boys younger than 1 yr of age. The presence of leukocyte esterase, >5 white blood cells/high-power field on a spun urine specimen, or bacteria detected by Gram stain on an unspun urine specimen suggests urinary tract infection, but the sensitivity of these indicators is, on average, only 75–85%; urine culture is the definitive test. Procalcitonin, C-reactive protein, and interleukin-6 are being investigated as potential biomarkers of differentiating serious bacterial illness from benign viral disease in children.

**MANAGEMENT**

Most patients who present to the pediatrician’s office with an acute illness will not require resuscitation. However, the pediatrician needs to be prepared to evaluate and begin resuscitation for the seriously ill or unstable child. The pediatrician’s office should be stocked with appropriate equipment necessary to stabilize an acutely ill child. Maintenance of that equipment and ongoing training of the office staff in use of the equipment and procedures is required (see Chapter 66). The evaluation must begin with assessment of the ABCs—airway, breathing, and circulation. When assessing the airway, chest rise should be evaluated, and evidence of increased work of breathing sought. The examiner should ensure that the trachea is midline. If the airway is patent and no signs of airway obstruction are present, the patient is allowed to assume a position of comfort. If the child shows signs of airway obstruction, repositioning of the head with the chin-lift maneuver may alleviate the obstruction. An oral or nasal airway may be necessary in patients in whom airway patency cannot be maintained. These devices are not well-tolerated in conscious patients and may induce gagging or vomiting, and instead are most often utilized to facilitate effective bag-valve-mask ventilation. Once airway patency has been established, the adequacy of breathing should be evaluated. Slow respiratory rates or cyanosis may signal respiratory failure. If the airway is patent but the child’s respiratory effort is inadequate, positive pressure ventilation via bag-valve-mask should be initiated. Oxygen should be administered to all seriously ill or hypoxic children via nasal cannula or face mask. Auscultation of the lung fields should assess for air entry, symmetry of breath sounds, and presence of adventitious breath sounds such as crackles or wheezes. Bronchodilator therapy can be initiated to alleviate bronchospasm. Racemic epinephrine is indicated for stridor at rest in a patient with croup. Once airway and breathing have been addressed, circulation must be evaluated. This involves assessment of cardiac output. Symptoms of shock include tachycardia, cool extremities, delayed capillary refill time, mottled or pale skin, and effortless tachypnea. Hypotension is a late finding in shock and indicates significant decompensation has already taken place.

Vascular access is necessary for volume resuscitation in patients with impaired circulation, and an intraosseous line should be considered early on if there is any difficulty in vascular access for a patient requiring resuscitation. Once an intervention is performed, the clinician must reassess the patient.

If the febrile child is older than 3 mo and appears well, if the history or physical examination does not suggest a serious illness, the child may be followed expectantly. This profile applies to most children with acute febrile illnesses. If, on the other hand, the child appears ill, or the history or physical examination suggests a serious infection, definitive laboratory tests appropriate for those findings are indicated (chest x-ray for a child with grunting). If advanced imaging is required (ultrasound or CT scan for suspected appendicitis), it may be prudent to defer such testing to pediatric specialty care if the decision has already been made to transport the child to a higher level of care. The area of greatest controversy is whether laboratory studies are needed in a febrile child who appears well and has no abnormalities on history and physical examination, but who is younger than 3 mo or whose temperature is high. Many would agree that a sepsis work-up is indicated in the febrile child younger than 1 mo and possibly in the febrile child who is as old as 3 mo.

**DISPOSITION**

The majority of children evaluated in the office for an acute illness can be managed on an outpatient basis. These patients should have reassuring physical examinations, stable vital signs, and adequate follow-up. A mildly dehydrated patient can be discharged to home for a trial of oral rehydration. Patients with a respiratory illness who are exhibiting signs of mild respiratory distress may be monitored at home with a repeat examination scheduled for the next day. Depending on the child’s status, the comfort of the parents, and the relationship of the family with the physician, telephone follow-up may be all that is necessary.

If the physician feels comfortable in following as an outpatient the child in whom no specific diagnosis has been established, a follow-up examination may yield the diagnosis. During the initial visit, or from one visit to the next during the acute illness, the change in symptoms or in the findings on physical examination over time may provide important diagnostic clues. For the child in whom a diagnosis has already been established and who does not require hospitalization, follow-up by telephone or an office visit should be used to monitor the course of the illness and to further educate and support the parents.

However, if it is deemed that the child needs a higher level of care, it is the pediatrician’s responsibility to decide what method of transfer is appropriate. Physicians may be reluctant to call for help because of a misperception that 911 services should be activated only for full-blown resuscitations. Emergency Medical Services (EMS) transport should be initiated for any child who is physiologically unstable (e.g., with severe respiratory distress, hypoxia, signs of shock, or altered mental status). If the family’s ability to comply promptly with
recommendation for emergency department evaluation is in question, that patient should also be transported by EMS. Some physicians and families may defer calling EMS because of the perception that a parent can get to the hospital faster by private car. Although rapidity of transport should be considered, the need for further interventions during transport and the risk of clinical decompensation are other important factors in the decision to activate EMS. Ultimately, the legal responsibility for choosing an appropriate level of transport for a patient lies with the referring physician, until responsibility of care is officially transferred to another medical provider.

*Bibliography is available at Expert Consult.*
Bibliography


The overwhelming majority of the 30 million children who present annually for emergency care in the United States are seen at community hospital emergency departments (EDs). Visits to children's hospital EDs account for just 11% of initial emergency care encounters. This distribution suggests that the greatest opportunity to optimize care for acutely ill or injured pediatric patients, on a population basis, occurs broadly as part of a systems-based approach to emergency services, an approach that incorporates the unique needs of children at every level. Conceptually, emergency medical services for children are characterized by an integrated, continuum of care model (Fig. 66-1). The model is designed such that patient care flows seamlessly from the primary care medical home through transport and on to hospital-based definitive care. It includes the following 5 principal domains of activity:

1. Prevention, primary and secondary
2. Out-of-hospital care, both emergency response and prehospital transport
3. Hospital-based care: ED and inpatient
4. Interfacility transport, as necessary, for definitive or subspecialty care (see Chapter 66.1)
5. Rehabilitation.

The federal Emergency Medical Services for Children (EMSC) program of the Health Resources and Services Administration's Maternal and Child Health Bureau has stewarded improvements in the care of children in the context of the continuum of care model. The programmatic mission of the EMSC program is as follows:

- To ensure state-of-the-art emergency medical care for the ill or injured child and adolescent.
- To ensure that pediatric services are well integrated into an emergency medical services system and backed by optimal resources.
- To ensure that the entire spectrum of emergency services—including primary prevention of illness and injury, acute care, and rehabilitation—is provided to infants, children, adolescents, and young adults.

EMSC funding to states and U.S. territories has created a national framework upon which necessary advances in education, advocacy, and research are taking place. EMSC grantees, constituents, and stakeholders as well as professional organizations such as the American Academy of Pediatrics are collaboratively engaged in implementation activities and projects that address the pediatric-specific recommendations stemming from the Institute of Medicine (IOM) report The Future of Emergency Care in the United States Health System.

**THE PRIMARY CARE PHYSICIAN AND OFFICE PREPAREDNESS**

The primary care physician (PCP) has multiple important roles in the emergency medical services system. Through anticipatory guidance, the PCP can help shape the attitudes, knowledge, and behaviors of parent and child, with the primary goal of preventing acute medical events, such as injury and status asthmaticus. The point of care initiation for many acute problems is often the PCP office. From the standpoint of personnel, equipment, training, and protocols, the PCP office setting must be adequately prepared to initially manage acute and emergency exacerbations of common pediatric conditions, such as respiratory distress and seizures. Furthermore, on rare occasion, the PCP office environment may be confronted with a child in clinical extremis who requires resuscitative intervention and stabilization. It is, therefore, incumbent upon the PCP not only to ensure access to emergency medical services (EMS), that is, 911 system activation, but also to ensure that there is adequate, onsite psychomotor skill preparation to deal with such an emergency. Office preparedness requires training and continuing education for staff members, protocols for emergency intervention, ready availability of appropriate resuscitation drugs and equipment, and knowledge of local EMS resources and ED capabilities.

**Staff Training and Continuing Education**

It is a reasonable expectation that all office staff, including receptionists and medical assistants, be trained in cardiopulmonary resuscitation (CPR) and that their certification be maintained on an annual basis. Nurses and physicians should also have training in a systematic approach to pediatric resuscitation. Core knowledge may be obtained through standardized courses in advanced life support (ALS) offered by national medical associations and professional organizations. Frequent recertification is important for knowledge retention and skill maintenance. Examples are the Pediatric Advanced Life Support (PALS) and Pediatric Emergency Assessment, Recognition and Stabilization (PEARS) courses sponsored by the American Heart Association, the Advanced Pediatric Life Support (APLS) course sponsored by the American Academy of Pediatrics (AAP) and the American
Protocols
Standardized protocols for telephone triage of seriously ill or injured children are essential. When a child's status is in question and prehospital care is available, ambulance transport in the care of trained personnel is always preferable to transport by privately owned vehicle. This obviates the potentially serious medical consequences of relying on unskilled and distraught parents without the ability to provide even basic life support (BLS) measures to an unstable child during transport to an ED. Practitioners can work with their local pediatric emergency care resource center (e.g., children's hospital or academic department of pediatrics) to develop and maintain written protocols for office-based management of a range of conditions, including anaphylaxis, cardiopulmonary arrest, head trauma, ingestions, shock, status asthmaticus, status epilepticus, and upper airway obstruction. Regular practice using mock code scenarios improves office-based practitioner confidence and self-efficacy in managing these problems.

Resuscitation Equipment
Availability of necessary equipment is a vital part of an emergency response. Every physician's office should have essential resuscitation equipment and medications packaged in a pediatric resuscitation cart or kit (Table 66-1). This cart or kit should be checked on a regular basis and kept in an accessible location known to all office staff. Outdated medications, a laryngoscope with a failed light source, or an empty oxygen tank represents a potential catastrophe in a resuscitation scenario. Such an incident can be easily avoided if an equipment checklist and maintenance schedule are implemented. A pediatric kit that includes posters, laminated cards, or a color-coded length-based resuscitation tape specifying emergency drug doses and equipment size is invaluable in avoiding critical therapeutic errors during resuscitation.

To facilitate emergency response when a child needs rapid intervention in the office, all personnel should have designated roles. Organizing a "code team" within the office ensures that necessary equipment is made available to the physician in charge, that an appropriate medical record detailing all interventions and the child's response is generated, and that the 911 call for EMS response or a transport team is made in a timely fashion.

Transport
Once the child has been stabilized, a decision must be made on how to transport a child to a facility capable of providing definitive care. If a child has required airway or cardiovascular support, has altered mental status or unstable vital signs, or has significant potential to deteriorate en route, it is not appropriate to send the child via privately owned vehicle, regardless of proximity to a hospital. Even when an ambulance is called, it is the PCP's responsibility to initiate essential life support measures and to attempt to stabilize the child before transport.

In metropolitan centers with numerous public and private ambulance agencies, the PCP must be knowledgeable about the level of service that is provided by each. The availability of BLS versus ALS services, the configuration of the transport team, and pediatric expertise vary markedly among agencies and across jurisdictions. BLS services provide basic support of airway, breathing, and circulation, whereas ALS units are capable of providing resuscitation drugs and procedural interventions as well. Some communities may have only BLS services available, whereas others may have a 2-tiered system, providing both BLS and ALS. It may be appropriate to consider medical air transport when definitive or specialized care is not available within an immediate community or when ground transport times are prolonged. In that case, initial transport via ground to an appropriate helicopter landing zone or a local hospital for interval stabilization may be undertaken, pending arrival of the air transport team. Independent of whether a child is to be transported by air or ground, copies of the pertinent medical records and any radiologic studies or laboratory results should be sent with the patient, and a call made to the physicians at the receiving facility to alert them to the referral and any treatments administered. Such notification is not merely a courtesy; direct physician-to-physician communication is essential to ensure adequate transmission of patient care information, to allow

<table>
<thead>
<tr>
<th>Table 66-1</th>
<th>Recommended Drugs and Equipment for Pediatric Office Emergencies</th>
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<tbody>
<tr>
<td><strong>DRUGS</strong></td>
<td>E</td>
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<tr>
<td>Oxygen</td>
<td>E</td>
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<tr>
<td>Albuterol for inhalation</td>
<td>E</td>
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<tr>
<td>Epinephrine (1:1,000)</td>
<td>E</td>
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<tr>
<td>Activated charcoal</td>
<td>E</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>S</td>
</tr>
<tr>
<td>Anticonvulsants (diazepam/oral)</td>
<td>S</td>
</tr>
<tr>
<td>Corticosteroids (parenteral/oral)</td>
<td>S</td>
</tr>
<tr>
<td>Diphenhydramine (parenteral, 50 mg/mL)</td>
<td>S</td>
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<tr>
<td>Epinephrine (1:10,000)</td>
<td>S</td>
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<tr>
<td>Atropine sulfate (0.1 mg/mL)</td>
<td>S</td>
</tr>
<tr>
<td>Naloxone (0.4 mg/mL)</td>
<td>S</td>
</tr>
<tr>
<td>Sodium bicarbonate (4.2%)</td>
<td>S</td>
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<tr>
<td><strong>INTRAVENOUS FLUIDS</strong></td>
<td>S</td>
</tr>
<tr>
<td>Normal saline (NS) or lactated Ringer solution (500-mL bags)</td>
<td>S</td>
</tr>
<tr>
<td>5% dextrose, 0.45 NS (500-mL bags)</td>
<td>S</td>
</tr>
<tr>
<td><strong>EQUIPMENT FOR AIRWAY MANAGEMENT</strong></td>
<td>E</td>
</tr>
<tr>
<td>Oxygen and delivery system</td>
<td>E</td>
</tr>
<tr>
<td>Bag-valve-mask (450-mL and 1,000-mL)</td>
<td>E</td>
</tr>
<tr>
<td>Clear oxygen masks, breather and non-rebreather, with reservoirs (infant, child, adult)</td>
<td>E</td>
</tr>
<tr>
<td>Suction device, tonsil tip, bulb syringe</td>
<td>E&amp;S</td>
</tr>
<tr>
<td>Nebulizer or metered-dose inhaler with spacer/mask</td>
<td>E&amp;S</td>
</tr>
<tr>
<td>Oropharyngeal airways (sizes 00-5)</td>
<td>E&amp;S</td>
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<tr>
<td>Pulse oximeter</td>
<td>E&amp;S</td>
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<tr>
<td>Nasopharyngeal airways (sizes 12-30F)</td>
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<tr>
<td>Magill forceps (pediatric, adult)</td>
<td>E&amp;S</td>
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<tr>
<td>Suction catheters (sizes 5-16F and Yankauer suction tip)</td>
<td>E&amp;S</td>
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<tr>
<td>Nasogastric tubes (sizes 6-14F)</td>
<td>E&amp;S</td>
</tr>
<tr>
<td>Laryngoscope handle (pediatric, adult) with extra batteries, bulbs</td>
<td>E&amp;S</td>
</tr>
<tr>
<td>Laryngoscope blades (straight 0-2; curved 2-3)</td>
<td>E&amp;S</td>
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<tr>
<td>Endotracheal tubes (uncuffed 2.5-5.5; cuffed 6.0-8.0)</td>
<td>E&amp;S</td>
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<tr>
<td>Stylets (pediatric, adult)</td>
<td>E&amp;S</td>
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<tr>
<td>Esophageal intubation detector or end-tidal carbon dioxide detector</td>
<td>E&amp;S</td>
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<tr>
<td><strong>EQUIPMENT FOR VASCULAR ACCESS AND FLUID MANAGEMENT</strong></td>
<td>E</td>
</tr>
<tr>
<td>Butterfly needles (19-25 gauge)</td>
<td>S</td>
</tr>
<tr>
<td>Catheter-over-needle device (14-24 gauge)</td>
<td>S</td>
</tr>
<tr>
<td>Arm boards, tape, tourniquet</td>
<td>S</td>
</tr>
<tr>
<td>Intravenous needles (16-, 18-gauge)</td>
<td>S</td>
</tr>
<tr>
<td>Intravenous tubing, micro-drip</td>
<td>S</td>
</tr>
<tr>
<td><strong>MISCELLANEOUS EQUIPMENT AND SUPPLIES</strong></td>
<td>E</td>
</tr>
<tr>
<td>Color-coded tape or preprinted drug doses</td>
<td>E</td>
</tr>
<tr>
<td>Cardiac arrest board/backboard</td>
<td>E</td>
</tr>
<tr>
<td>Sphygmomanometer (infant, child, adult, thigh cuffs)</td>
<td>E</td>
</tr>
<tr>
<td>Splints, sterile dressings</td>
<td>E</td>
</tr>
<tr>
<td>Automated external defibrillator with pediatric capabilities</td>
<td>E&amp;S</td>
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<tr>
<td>Spot glucose test</td>
<td>S</td>
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<tr>
<td>Stiff neck collars (small/large)</td>
<td>S</td>
</tr>
<tr>
<td>Heating source (overhead warmer/infrared lamp)</td>
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</tr>
</tbody>
</table>

E, essential; S, strongly suggested.

mobilization of necessary resources in the ED, and to redirect the transport if the emergency physician believes that the child would be more optimally treated at a facility with specialized services.

**PEDICATRIC PREHOSPITAL CARE**

Prehospital care refers to emergency assistance rendered by trained emergency medical personnel before a child reaches a treating medical facility. The goals of prehospital care are to further minimize systemic insult or injury through a series of well-defined and appropriate interventions and to embrace principles that ensure patient safety. Most communities in the United States have a formalized EMS system; the organizational structure and nature of emergency medical response depend greatly on local demographics and population base. EMS may be provided by volunteers or career professionals working in a fire-based or independent “third service” response system. Key points to recognize in negotiation of the junction between the community physician and the local EMS system include access to the system, provider capability, and destination determination.

**Access to the EMS System**

Virtually all Americans have access to the 911 telephone service that provides direct access to a dispatcher who coordinates police, fire, and EMS responses. Some communities have an enhanced 911 system, in which the location of the caller is automatically provided to the dispatcher, permitting emergency response even if the caller, such as a young child, cannot give an address. The extent of medical training for these dispatchers varies among communities, as do the protocols by which they assign an emergency response level (BLS vs ALS). In some smaller communities, no coordinated dispatch exists, and emergency medical calls are handled by the local law enforcement agency.

When activating the 911 system, the physician must make clear to the dispatcher the nature of the medical emergency and the condition of the child. In many communities, emergency medical dispatchers are trained to ask a series of questions per protocol that determines the appropriate level of provider to be sent.

**Provider Capability**

There are many levels of training for prehospital EMS providers, ranging from individuals capable of providing only first aid to those trained and licensed to provide ALS. All EMS personnel, whether basic or emergency medical technicians (EMTs) or paramedics, receive training in pediatric emergencies; however, pediatric cases actually constitute roughly 10% of all EMS transports.

First responders may be law enforcement officers or firefighters, who are dispatched to provide emergency medical assistance, or bystanders. Public safety personnel have a minimum of 40 hr of training in first aid and CPR. Their role is to provide rapid response and stabilization pending the arrival of more highly trained personnel. In some smaller communities, this may be the only prehospital emergency medical response available.

In the United States, the bulk of emergency medical response is provided by EMTs, who may be volunteers or paid professionals. Basic EMTs may staff an ambulance after undergoing a training program of approximately 100 hr. They are licensed to provide BLS services but may receive further training in some jurisdictions to expand their scope of practice to include intravenous catheter placement and fluid administration, management of airway adjuncts, and the use of an automated external defibrillator.

Paramedics, or EMT-Ps, represent the highest level of EMT response, with medical training and supervised field experience of approximately 1,000 hr. Paramedic skills include advanced airway management, including endotracheal intubation; placement of peripheral, central, or intravenous lines; intravenous administration of drugs; administration of nebulized aerosols; needle thoracostomy; and cardioversion and defibrillation. These professionals provide ALS services, functioning out of an ambulance equipped as a mobile intensive care unit. In a joint policy statement entitled Equipment for Ground Ambulances, the AAP, the ACEP, the American College of Surgeons Committee on Trauma, EMSC, the ENA, the National Association of EMS Physicians, and the National Association of EMS Officials have published guideline standards for essential ambulance equipment, medications, and supplies necessary to provide BLS and ALS care across the age spectrum. This essential equipment list represents one of the reference standards that the federal EMSC program has adopted as a performance measure for state-level operational readiness to care for children in an EMS system.

Both basic EMTs and paramedics function under the delegated licensing authority of a supervisory EMS medical director. This physician or a group of prehospital practice is broadly characterized under the umbrella term medical control. Direct, or online, medical control refers to medical direction either at the scene or in real time via voice or video transmission. Indirect, or offline, medical control refers to the administering of medical direction prior to and after the provision of care. Offline activities, such as provider education and training, protocol development, and medical leadership of quality assurance/quality improvement programs, represent areas in need of greater pediatric input. As a measure of the degree to which EMSC permanence is being established in state EMS systems, the federal EMSC program has required demonstration of participation in online and offline medical direction activities for pediatric patients and the seating of an EMSC advisory committee at the state level. These advisory bodies are well positioned to support EMS agencies in their pediatric readiness as well as provide a forum for the active engagement of pediatric care experts at a system level.

**Destination Determination**

The destination to which a pediatric patient is transported may be defined by parental preference, provider preference, or jurisdictional protocol, which is typically predicated on field assessment of anatomic and physiologic criteria and, in the case of trauma, mechanism of injury. In communities served by an organized trauma or regionalized EMS system that incorporates pediatric designation based on objectively verified hospital capabilities, seriously ill or injured children may be triaged by protocol to the highest-level center reachable within a reasonable amount of time. The mantra is to deliver the child to the “right care in the right time,” even if it requires bypassing closer hospitals. An exception is the child in full arrest, for whom expeditious transport to the nearest facility is always warranted. In 2012, modification of the Centers for Disease Control and Prevention’s national field trauma triage guidelines included a refinement of age-specific vital sign assessment criteria to more accurately reflect the unique physiologic response to injury in children. The Centers for Disease Control and Prevention guidelines are a valuable resource for pediatricians involved in EMS medical direction and are accessible as a multipurpose toolkit, including an educational webinar and downloadable mobile application, at http://www.cdc.gov/fieldtriage.

Regionalization in the context of EMS is defined as a geographically organized system of services that ensures access to care at a level appropriate to patient needs while maintaining efficient use of available resources. This system concept is especially germane in the care of children, given the relative scarcity of facilities capable of managing the full range and scope of pediatric conditions (Fig. 66-2). Regionalized systems of care coordinated with emergency medical dispatch, field triage, and EMS transport have demonstrated efficacy in improving outcomes for pediatric trauma patients, especially for younger children and for children with isolated head injury. Emerging evidence also suggests a similar benefit conferred to children in shock identified in the field who are preferentially transported to hospital EDs with documented pediatric ALS capability. The existence of statewide or regional standardized systems that formally recognize hospitals able to stabilize and/or manage pediatric medical emergencies is another federal EMSC performance measure against which operational capacity to provide optimal pediatric emergency care in this country is currently being judged.

In communities that do not have a hospital with the equipment and personnel resources to provide definitive pediatric inpatient care, interfacility transport of a child to a regional center should be undertaken after initial stabilization (see Chapter 66.1). When interfacility
transport is to be undertaken, indications for transfer, parental consent for transfer, and acceptance of the patient by the receiving physician must all be clearly documented in the medical record.

The ability of hospital EDs to respond to the emergency care of children varies and depends on a number of factors in addition to availability of equipment and supplies. Training, awareness, and experience of the staff as well as access to pediatricians and medical and surgical subspecialists also play a key role. The majority of children who require emergency care are evaluated in community hospitals by physicians, nurses, and other healthcare providers with variable degrees of pediatric training and experience. Although children account for 25-30% of all ED visits, only a fraction of these encounters represent true emergencies. Because the volume of critical pediatric cases is low, emergency physicians and nurses working in community hospitals often have limited opportunity to reinforce their knowledge and skills in the assessment of ill or injured children and in pediatric resuscitation. General pediatricians from the community may be consulted when a seriously ill or injured child presents to the ED, and they should have a structured approach to the initial evaluation and treatment of an unstable child of any age, regardless of the underlying diagnosis. Early recognition of life-threatening abnormalities in oxygenation, ventilation, perfusion, and central nervous system function and rapid intervention to correct those abnormalities are key to successful resuscitation and stabilization of the pediatric patient.

In its report The Future of Emergency Care in the U.S. Health System, the IOM strongly recommended that hospitals and EMS systems appoint qualified coordinators for pediatric emergency care, a recommendation consistent with pediatric emergency readiness guidelines advocated by the AAP and ACEP. Only 18% of EDs in the United States currently appoint a physician coordinator, and 12% appoint a nursing coordinator for pediatric emergency care. EDs that do appoint these positions tend to be more prepared as measured by compliance with nationally published guidelines on the care of children in the ED.

Minimum standards must be met by community EDs to ensure that children receive the best emergency care possible. Updated guidelines for the care of children in the ED have been published, reaffirmed and are endorsed by the AAP, the ACEP, and the ENA. These guidelines provide current information on policies, procedures, protocols, quality assurance methods, and equipment and supplies considered essential for managing pediatric emergencies. Specific recommendations on equipment, supplies, and medications for the ED are listed and updates are available on the AAP website. Table 66-2 lists sample policies, procedures, and protocols specifically addressing the needs of children in the ED.

The way in which the family supports the child during a crisis and, consequently, how the family is supported in the ED when caring for the child are critical to patient recovery, family satisfaction, and

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**Table 66-2** Guidelines for Pediatric-Specific Policies, Procedures, and Protocols for the Emergency Department

<table>
<thead>
<tr>
<th>Topic</th>
<th>Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illness and injury triage</td>
<td>Pediatric patient assessment and reassessment</td>
</tr>
<tr>
<td></td>
<td>Documentation of pediatric vital signs, abnormal vital signs, and actions to be taken for abnormal vital signs</td>
</tr>
<tr>
<td></td>
<td>Immunization assessment and management of the underimmunized patient</td>
</tr>
<tr>
<td></td>
<td>Sedation and analgesia for procedures, including medical imaging</td>
</tr>
<tr>
<td></td>
<td>Consent (including situations in which a parent is not immediately available)</td>
</tr>
<tr>
<td></td>
<td>Social and mental health issues</td>
</tr>
<tr>
<td></td>
<td>Physical or chemical restraint of patients</td>
</tr>
<tr>
<td></td>
<td>Child maltreatment (physical and sexual abuse, sexual assault, and neglect) mandated reporting criteria, requirements, and processes</td>
</tr>
<tr>
<td></td>
<td>Death of the child in the emergency department</td>
</tr>
<tr>
<td></td>
<td>Do-not-resuscitate orders</td>
</tr>
</tbody>
</table>

**Family-centered care, including:**
1. Involving families in patient care decision-making and in medication safety processes.
2. Family presence during all aspects of emergency care, including resuscitation.
3. Education of the patient, family, and regular caregivers.
4. Discharge planning and instruction.
5. Bereavement counseling.

**Communication with patient’s medical home or primary healthcare provider**

Medical imaging policies that address age- or weight-appropriate dosing for children receiving studies that impart ionizing radiation, consistent with ALARA (as low as reasonably achievable) principles

All-hazard disaster preparedness plan that addresses the following pediatric issues:
1. Availability of medications, vaccines, equipment, and appropriately trained providers for children in disasters.
2. Pediatric surge capacity for both injured and noninjured children.
3. Decontamination, isolation, and quarantine of families and children of all ages.
4. A plan that minimizes parent-child separation and includes system tracking of pediatric patients, allowing for the timely reunification of separated children with their families.
5. Access to specific medical and mental health therapies, as well as social services, for children in the event of a disaster.
6. Disaster drills, which should include a pediatric mass casualty incident at least every 2 yr.
7. Care of children with special healthcare needs.
8. A plan that includes evacuation of pediatric units and pediatric specialty units.

the mitigation of posttraumatic stress. Commitment to patient- and family-centered care in the ED ensures that the patient and family experience guides the practice of culturally sensitive care and promotes patient dignity, comfort, and autonomy. In the ED setting, particular issues, such as family presence, deserve specific attention. Surveys of parents have indicated that most want to be with their child during invasive procedures and even during resuscitation. Allowing their presence has been shown to reduce parental and patient anxiety and does not interfere with procedure performance. Patient- and family-centered care is also associated with improved care quality and patient safety.

EMERGING ISSUES IN EMSC

Of the pediatric-specific recommendations promulgated by the IOM in its widely publicized 2006 report on the future of emergency care, 3 have emerged as especially important for EMSC. The first deals directly with increased federal funding for the EMSC program, which supports more than 80 grantees with an established presence in 49 states, 5 U.S. territories, the District of Columbia, and the freely associated states of Micronesia, Palau, and the Marshall Islands. The grant awards cover 5 distinct funding categories ranging from basic science and clinical investigation to public sector capacity-building programs to national technical assistance centers to multicenter trials conducted within a large research network. Through the diversity of activity generated within the program, and in collaboration with stakeholders, the EMSC program affords synergistic opportunity to further the progress realized in the programs’ first 30 yr of existence. A tumultuous appropriations history not-with-standing, including several years of budget elimination, Congressional reauthorization, due in 2014, and will ensure stability for the EMSC program at least in the near term.

In addition to EMSC resource support, the IOM also recommended that (a) federal agencies in partnership with state and regional planning bodies and emergency care provider organizations convene a panel with multidisciplinary expertise to develop strategies for addressing pediatric needs in the event of a disaster, and (b) the U.S. Department of Health and Human Services conduct a study to examine the gaps and opportunities in emergency care research, including pediatric emergency care, and recommend a strategy for the optimal organization and funding of the research effort. Both of these recommendations have generated activity of significant import to the emergency care community, EMSC specifically, and warrant mention.

Disaster Preparedness

Children constitute approximately 30% of the population; in a catastrophic event, natural or human-made, several unique factors place children at disproportionate, increased risk. During the day large groups of children are typically cohorted, separate from their families, in schools and daycare centers where mass casualties can easily occur and reunification is challenging. Furthermore, in the event of a biologic or chemical attack, unique anatomic, developmental, and physiologic features make children especially vulnerable to absorption and/or inhalation of toxic agents. Following the broad pediatric impact of the devastating Gulf Coast hurricanes Katrina and Rita in the mid-2000s, Congress established the National Commission on Children and Disasters. The Commission’s mandate was to conduct a comprehensive study to examine and assess the needs of children as they relate to preparation for, mitigation of, response to, and recovery from all hazards, including major disasters and emergencies. The findings and recommendations of the Commission’s 2010 report to the President and to Congress have established a broad framework for ongoing preparedness efforts related not only to child physical health, but also, importantly, to behavioral and emotional well-being. In addition, pertinent resources related to pediatric-focused areas of concerns such as evacuation, separation-reunification, sheltering, countermeasures, surge capacity and triage are being monitored and chronicled under the PEDPrepared Disaster Clearinghouse at the EMSC National Resource Center website, http://www.emscnrc.org/pedprepared.

Bibliography is available at Expert Consult.

66.1 Interfacility Transport of the Seriously Ill or Injured Pediatric Patient

Elizabeth A. Edgerton and Bruce L. Klein*

Patients often seek treatment at facilities that lack sufficient expertise to treat their conditions, necessitating transfer to more appropriate specialty centers. This is especially pronounced in pediatrics. EMS providers or parents usually take children to local EDs first, where their conditions and physiologic stabilities are assessed. Although bringing a child directly to the local ED may be proper logistically, local EDs can be less than ideal for pediatric emergencies. Children account for 27% of all ED visits but only 6% of EDs have all the necessary supplies for pediatric emergencies. Also, general EDs are less likely to have pediatric expertise or policies in place for the care of children. Outcomes for critically ill children treated in pediatric intensive care units (PICUs) are better than for those treated in adult ICUs. When pediatric critical care is required, transport to a regional PICU is indicated. In addition, often the type of subspecialty care needed (e.g., pediatric orthopedics) is available only at the pediatric center.

Pediatric transport medicine consists of the interfacility transfer of infants, children, and adolescents from community facilities to pediatric centers that can provide the needed level of expertise. Transport is performed by professionals proficient in pediatric transport on specially age-equipped ground, rotorcraft, or fixed-wing ambulances. Pediatric transport medicine is a multidisciplinary field comprising pediatric critical care and pediatric emergency medicine physicians (and, sometimes for very young infants, neonatologists); nurses, respiratory therapists, and paramedics with advanced training for pediatric transport; and communications specialists. The goal is to deliver quality pediatric care to the region’s children, while optimizing the use of regional resources. For the individual child, the aim is to stabilize and, when appropriate, begin treating as soon as possible—that is, at the local ED and during transport, well before arrival at the referral center.

The AAP Section on Transport Medicine, the Association of Air Medical Services, the Federal Aviation Administration (FAA), and others have published recommendations regarding transport programs. Models for pediatric transport services vary depending on the needs and available resources in a geographic region, but all should have certain basic components: a network of community hospitals and regional pediatric centers; an established communications and dispatch system that easily facilitates transfer to the pediatric center; ground and/or air ambulances; medical and nursing leadership from pediatric critical care or pediatric emergency medicine (or neonatology); experienced pediatric medical control physicians (MCPs); a multidisciplinary team of pediatric transport professionals specially trained to provide the appropriate level of care required during transport; operational and clinical policies and procedures that guarantee safe, state-of-the-art, and timely pediatric critical care transport; and a database for quality and performance assessment.

COMMUNICATIONS AND DISPATCH CENTER

Communications are one of the most vital components of a regional transport system. Treating a critically ill or injured child is an uncommon event for most community physicians. Therefore, they need to know whom, how, and when to call for assistance in the stabilization and transfer of a pediatric patient. The communications and dispatch center provides a single telephone number for such calls.

The communications and dispatch center coordinates communications among the outlying facility, receiving unit, MCP, transport team, and others. This center may be part of a hospital unit (e.g., ED, PICU), self-contained in a single institution (e.g., Emergency Communications and Information Center), or based offsite as a freestanding center coordinating communications and dispatch for multiple transport programs.

Staffing varies depending on the type of center. On-duty nurses or physicians may receive calls at unit-based models with low volumes.

*Adapted initially from Dr. Lorry R. Frankel's chapter in the 18th edition of this book.
Bibliography

American Academy of Pediatrics; American College of Emergency Physicians; American College of Surgeons, Committee on Trauma; Emergency Medical Services for Children; Emergency Nurses Association; National Association of EMS Physicians; National Association of State EMS Officials: Joint policy statement—equipment for ground ambulances, Prehosp Emerg Care 18:92–97, 2014.


In contrast, dedicated communications specialists usually staff self-contained or freestanding centers, which tend to be busier. The communications specialist has numerous responsibilities, including answering the referring physician's call promptly; documenting essential patient demographic information; arranging for immediate consultation with the MCP; dispatching the transport team to the referring facility expeditiously; updating the referring facility with any changes in the arrival time; and coordinating medical control and other necessary transport-related calls. The transport team must be equipped with a cellular telephone or radio for immediate contact with the referring and referring facilities.

**MEDICAL CONTROL PHYSICIAN**

The MCP is involved in the clinical care and safe transport of the patient from the time of referral through arrival at the receiving hospital unit. The MCP's oversight increases once the transport team arrives at the referring facility. The MCP should have expertise in pediatric critical care or pediatric emergency medicine (or sometimes neonatology). Besides having the knowledge required to stabilize a critically ill or injured child, the MCP must be familiar with the transport environment; the transport team members’ capabilities; the program's policies and procedures; and the region's geography, medical resources, and regulations regarding interhospital transport. The MCP must possess good interpersonal and communication skills and must be able to maintain collegiality with the referring hospital's staff during a potentially difficult and stressful situation.

Once a transport call is received, the MCP must be immediately available to confer with the referring physician. Although the MCP may have other responsibilities, these transport responsibilities take priority in order to avoid undue delays when transferring a critically ill child. Often the MCP recommends further testing or therapeutic interventions that can be delivered by the referring hospital before the transport team arrives. The MCP may seek additional guidance from other specialists, as necessary. Because the child's condition may change rapidly, the MCP must remain ready to give additional advice. All conversations and recommendations regarding the care of the patient should be documented. Some centers record these conversations.

After discussion with the referring physician—and, when warranted, with the transport staff—the MCP determines the best team composition and vehicle for transport. The MCP usually does not accompany the team but remains available, by phone or radio, to supervise care.

**TRANSPORT TEAM**

Transport team composition varies among programs—and sometimes within an individual program. The team's composition is based on a variety of factors, including the severity of the child's illness or injury; the distance to the referring facility; the team members' advanced practice abilities; the referrer's (reasonable or unreasonable) insistence that a physician be present; the program's historical professional makeup; and the region's staffing regulations. The team should be composed of physicians, nurses, respiratory therapists, and/or paramedics who have expertise in pediatric critical care or pediatric emergency medicine (or neonatology in some cases), as well as advanced education and training in those cognitive and procedural areas important for pediatric critical care transport. There is a lower incidence of transport-related morbidity for critically ill and injured children transported by pediatric specialty teams than for those transported by generalist teams.

Various scoring systems have been developed to predict the need for a physician during transport. It seems that a team member’s training, experience, and skill in treating critically ill patients are more important considerations than that team member’s professional degree. Team members must understand basic pediatric pathophysiology and collectively must be able to assess and monitor a critically ill or injured child; manage the airway and provide respiratory support; obtain vascular access; perform point-of-care testing; and administer those medications commonly used in pediatric critical care transport. They must be familiar with the physiologic alterations as well as practical difficulties of the transport environment and, importantly, must be comfortable working in an out-of-hospital setting. Physicians are less often deployed on transport teams in part because of the advanced training that other healthcare professionals on the transport team receive.

The transport team should have a designated team leader who, in addition to the team leader's many other responsibilities, interacts with the MCP during the transport. Once the team arrives at the referring facility, the team should reassess the child’s condition, review all of the pertinent diagnostic studies and therapies, and discuss the situation with the referring staff and parents. If the patient's condition has changed significantly, the team leader may need to contact the MCP for additional advice. Otherwise, the team leader should generally notify the MCP before starting to bring the child to the receiving facility. Any care delivered by the team during transport should be documented, and copies of all medical records—including laboratory data, radiographs, and scans—should accompany the child to the pediatric center. The receiving unit must be updated prior to arrival so it can finalize preparations for the patient.

**GROUND VERSUS AIR AMBULANCE**

Transport options include ground, rotorcraft, and fixed-wing ambulances. Vehicle selection depends on the child's emergency needs; transport team's capabilities; any out-of-hospital staffing or equipment requirements (e.g., for extracorporeal membrane oxygenation, inhaled nitric oxide or heliox); referring facility's abilities; distance; terrain; traffic patterns; ground or air ambulance availability; helicopter landing pad or airport access; weather conditions; and expense.

The transport vehicle must be equipped with electrical power, oxygen, and suction and must have sufficient space for the equipment and supplies that the team brings along—stretcher or isolette, monitor, ventilator, oxygen tank(s), medication pack(s), infusion pumps, and more. Compared with helicopters, ambulances are more spacious and able to carry more weight, so they can accommodate larger teams and more equipment. Another advantage of ground ambulance transport is the ability to stop en route if the patient’s condition deteriorates; this feature greatly facilitates the performance of certain interventions, such as intubation.

An airplane may be able to fly to an area where distance (>150 miles), altitude, or weather precludes helicopter use. However, the use of an airplane necessitates several ambulance transfers, with their attendant delays and potential complications. There are also delays when the plane must fly from a remote base to the program’s jurisdiction.

**TRANSPORT PHYSIOLOGY**

When possible, the transport team tries to provide the same care during transport as the patient would receive in the specialty center. This can be difficult, though, because of limitations in personnel, equipment, and space, as well as other environmental challenges.

The team and child are subjected to variable intensities of background noise and vibration while traveling in the vehicle cabin. Noise can impair the team’s ability to auscultate breath sounds, heart sounds, and blood pressure, another reason for monitoring vital signs mechanically and relying on other assessment modalities, such as the level of mentation, skin color, and capillary refill. To mitigate noise, the helicopter crew and patient should wear helmets or headphones (or another wearable noise attenuator such as MiniMuffs [Natus Medical Incorporated, San Carlos, CA]). Motion and vibration can lead to increased metabolic rate, shortness of breath, and fatigue in the patient, as well as motion sickness in the patient and staff.

On fixed- or certain rotary-wing transports, the patient may suffer adverse physiologic effects from altitude. With increasing altitude, the barometric (atmospheric) pressure decreases and gases expand. As the barometric pressure drops and gas expands, the partial pressures of ambient oxygen (P\text{O}_2) and, consequently, arterial oxygen (P\text{A}_O_2) decrease. For example, at 8,000 feet—an elevation at which unpressurized airplanes may fly, as well as the effective cabin altitude for many pressurized airplanes flying at 35,000 to 40,000 feet—the barometric pressure, P\text{O}_2, P\text{A}_O_2, and arterial oxygen saturation fall to 565 mm Hg, 118 mm Hg, 61 mm Hg, and 93%, respectively. (In comparison, the barometric pressure, P\text{O}_2, P\text{A}_O_2, and arterial oxygen saturation are...
760 mm Hg, 159 mm Hg, 95 mm Hg, and 100% at sea level.) Although healthy individuals usually tolerate these changes well, patients with respiratory insufficiency, significant blood loss, or shock may decompensate and should receive supplemental oxygen.

Gases expand 10-15% at the few thousand feet at which helicopters typically fly, and approximately 30% at 8,000 feet. Gases within the body itself also expand as the altitude increases. Gas expansion must be appreciated during transport via air of a patient with a pneumocephalus, pneumothorax, bowel obstruction, or another condition involving entrapped gas. Prior to transport, a pneumothorax should be decompressed, and a nasogastric tube inserted for ileus.

SAFETY
Safety is of paramount importance and mandates constant vigilance by everyone involved. Accident rates for pediatric air and ground transport are estimated at approximately 1/1,000 transports. The team should routinely attend pilot briefs, as well as perform safety inspections of the vehicles and equipment, aided by checklists. When in doubt, the MCP should solicit input from the staff about whether to transport via air or ground ambulance or to employ lights and sirens, decisions that cannot be taken lightly. The pilot’s or driver’s judgment as to the safety of proceeding during inclement weather or with a mechanical problem must not be overruled.

Organizations, such as the FAA and the National Transportation Safety Board, play a role in ensuring safe interfacility transport. The Commission on Accreditation of Medical Transport Systems (CAMTS) is an independent, peer review organization that was established in 1990 in response to the number of air medical accidents in the 1980s. CAMTS, through voluntary participation, audits and accredits fixed-wing, rotary-wing, and ground interfacility medical transport services.

FAMILY-CENTERED CARE
Family-centered care represents a philosophy that respects the important role that family members play in a child’s care. It recognizes family members and healthcare providers as partners in caring for the child. Family presence during transport is beneficial because it provides support to children in stressful situations and assists healthcare providers in delivering care to patients with complex and/or chronic medical problems.

As care is transitioned from the referring hospital, it is the transport team’s responsibility to maintain family-centered care. The team meets with family members to explain the transport process, obtain consent, and discuss anticipated management. When possible, the transport team should attempt to accommodate a family member’s presence onboard. However, the family member and child may need to be separated when the child is critically ill and rapid transport is essential, or if there is space or weight limitations in the air or ground ambulance. In these situations, it is important that family members have a clear understanding of how the child will be cared for during the separation.

REFERRING HOSPITAL RESPONSIBILITIES
Transfer of a patient to another facility requires written documentation by the referring physician of the need and reasons for transfer, including a statement that the risks and benefits, as well as any alternatives, have been discussed with the parents. The parent’s informed consent to the transfer should be obtained.

Federal law under the Emergency Medical Treatment and Active Labor Act (EMTALA), part of the Consolidated Omnibus Budget Reconciliation Act (COBRA), imposes specific requirements that a patient presenting to an ED be given a medical screening examination without regard to ability to pay. If upon examination an emergency medical condition is found, the hospital is required to stabilize the patient or to transfer the patient to another facility if unable to stabilize the patient or if requested by the patient. The primary requirement is that the referring physician must certify that the medical risks of transfer are outweighed by its potential benefits. The receiving hospital must agree to accept the patient and have the space and staff to provide the necessary treatment. The transferring hospital is responsible for arranging for the transfer and ensuring that it is performed by qualified medical personnel with appropriate equipment. It must send copies of the patient’s medical records and test results, even those that become available after the transfer is complete.

Some referring hospitals have entered into transfer agreements with specialty centers in the interests of facilitating the smooth and safe transfer of the pediatric patient. Having prepared forms for all of the above purposes also aids in the transfer process.

Each hospital needs to review its facility’s guidelines, and if established guidelines do not exist the EMSG, in partnership with the Emergency Nurses Association and the Society of Trauma Nurses, has developed the “Inter Facility Transfer Tool Kit for the Pediatric Patient” (available at www.pediatricreadiness.org). This tool kit includes the essentials for comprehensively and safely transferring the pediatric patient to the most appropriate level of care in a timely manner.

EDUCATIONAL OUTREACH
Besides safe and rapid transport, regional pediatric transport programs (and their specialty centers) have an obligation to provide educational opportunities to community healthcare providers so that these providers can acquire the necessary skills to evaluate and stabilize a critically ill or injured child until the transport team arrives. These learning activities may include transport case reviews; lectures on pediatric acute care topics; resuscitation programs such as the PALS course, APLS course, and S.T.A.B.L.E. (sugar and safe care, temperature, airway, blood pressure, lab work, emotional support) program; and rotations through the specialty center’s pediatric ED and PICU. These activities also help cement relationships with the referring facility’s staff.

Bibliography is available at Expert Consult.

66.2 Outcomes and Risk Adjustment
Evaline A. Alessandrini

Health services research has documented wide variation in the likelihood that patients receive quality, evidence-based healthcare, and this can negatively impact the health of children and youth. The complexities of delivering high-quality healthcare are magnified in the ED. Patients are in crisis, EDs are often overcrowded, patient–physician relationships are based on brief interactions, and the variety of complaints and diagnoses is immense.

OUTCOME MEASURES IN EMERGENCY MEDICAL SERVICES FOR CHILDREN
Emergency Care for Children: Growing Pains, one report of the 2007 IOM series on the future of emergency care, recommends that pediatric emergency medical systems specifically support the development of national standards for emergency care performance measurement. The Donabedian structure–process–outcome model has set the framework for most contemporary quality measurement and improvement activities. Structural elements provide indirect quality-of-care measures related to a physical setting and resources. Process indicators provide a measure of the quality of care and services by evaluating the method or process by which care is delivered, including both technical and interpersonal components. Outcome elements describe valued results related to lengthening life, relieving pain, reducing disabilities, and satisfying the consumer.

Defining relevant outcomes for pediatric emergency care is difficult. A true “outcome-based” approach describes observable measures such as mortality, risk of organ system failure, and disability. An alternative approach is a “resource-based” outcome measure definition related to the level of care required. Children who are more ill, in general, require more resources. Thus, resource use across groups of patients reflects relative severity of illness in the groups. Examples of resource-based outcomes include need for hospital admission (ED disposition), ED
Bibliography


**Table 66-3** Stakeholder-Endorsed Outcome Measures for Pediatric Emergency Care

- Overall patient satisfaction with ED visit—nurses
- Overall patient satisfaction with ED visit—physicians
- Parent/caregiver understanding of ED discharge instructions
- ED length of stay for patients <18 yr of age
- Percentage of patients <18 yr of age left without being seen (LWBS)
- Effective pediatric procedural sedation
- Acute fracture patients with documented reduction in pain within 90 min of ED arrival
- Improvement in asthma severity score for patients with acute exacerbations
- ED revisit within 48 hr resulting in admission
- Medication error rates
- Global sentinel never events
- Unplanned return visit within 72 hr for the same/related asthma exacerbation
- Failure to achieve seizure control within 30 min of ED arrival
- Return visits within 48 hr resulting in admission for all urgent and emergency patients

**Table 66-4** Elements of the PRISA II Score

- Age <90 days
- Minor injury
- Abdominal pain in an adolescent
- Immunodeficiency
- Indwelling medical device
- Controller asthma medication
- Referral status
- Temperature
- Decreased mental status
- Low systolic blood pressure (<70 neonates and infants; <83 children; <100 adolescents)
- High diastolic blood pressure (>59 neonates and infants; >70, children; >90 adolescents)
- Low serum bicarbonate value (<20 mEq/L)
- High potassium value (>4.9 mEq/L)
- High blood urea nitrogen value (>80 mg/dL)
- High white blood cell count (>20,000/mm³)
- Oxygen therapy other than during inhaled bronchodilator treatments
- Low bicarbonate and high potassium values

**Table 66-5** Elements of the RePEAT Score

- Age
- Chief complaint
- Triage category
- Current use of prescription medications
- Arrival via EMS (ground/air)
- Heart rate
- Respiratory rate
- Temperature

length of stay, costs, and diagnostic and therapeutic interventions performed in the ED. Table 66-3 provides a list of outcome measures for pediatric emergency care developed by EMSC stakeholders during 2 separate consensus meetings.

**RISK ADJUSTMENT**

Measuring outcomes offers opportunities for EDs and other components of the healthcare system to make effective improvements over time, benchmark, and compare their end results with those of other institutions. Meaningful comparisons between EDs or within an ED over time generally require risk adjustment, which accounts for patient-related attributes such as age, or for preexisting conditions associated with the outcome of interest. Risk-adjustment “levels the playing field,” so that comparison of outcomes is as fair and meaningful as possible. Because children present to EDs with illnesses of varying acuity, ranging from rashes and colds to cardiac arrest, there is an inextricable linkage of severity to outcomes. Severity typifies the concept of “risk”—the higher the severity, the higher the risk of a given outcome. Without risk adjustment, EDs with sicker patients may appear to have worse outcomes.

A large number of instruments have been developed to adjust for severity or risk in clinical research and quality improvement activities. The commonly used PRISM (Pediatric Risk of Mortality) score is not well-suited for EMSC, given the extremely low rate of mortality. Several disease-specific acuity scoring systems are available for use in EMSC. The majority of these are intended for use in trauma patients, including the Injury Severity Score, Trauma Score, and Pediatric Trauma Score.

**RISK ADJUSTMENT TOOLS IN EMSC**

The choice of a risk-adjustment tool depends on several factors, including the population under study, the setting, and the outcomes of interest. Two risk-adjustment tools have been developed specifically for pediatric emergency medicine, the second-generation Pediatric Risk of Admission (PRISA II) score and the Revised Pediatric Emergency Assessment Tool (RePEAT).

**Pediatric Risk of Admission II**

PRISA II uses components of acute and chronic medical history and physiology to determine the probability of hospitalization. The outcome measure of interest is mandatory hospital admission (admissions utilizing therapies best delivered on an inpatient basis). Table 66-4 lists the patient-related attributes contributing to the PRISA II risk-adjustment score. Analytic models including the PRISA II score have good calibration (how well the probabilities predicted from the model correlated with the observed outcomes in the population) and discrimination (the ability to categorize subjects correctly into the categories of interest) with respect to mandatory hospital admission. Construct validity of the PRISA score was demonstrated by measuring the rates of the secondary outcomes: mandatory admission, PICU admission, and mortality. As the probability of hospital admission rose, the proportion of patients with these increasing care requirements also increased. This finding strongly supports the use of the PRISA II score as a valid measure of severity of illness. In addition, PRISA II was found to demonstrate racial/ethnic differences in severity-adjusted hospitalization rates, and also demonstrated that teaching hospitals had higher than expected severity-adjusted admission rates in comparison with non-teaching hospitals.

**Revised Pediatric Emergency Assessment Tool**

The RePEAT uses a limited set of data collected at the time of triage to model severity of illness as reflected by the level of care provided in the ED. This tool was developed to predict the level of care provided—routine assessment (clinical examination only ± nonprescription medicine), specific ED care (ED diagnostics and/or therapeutics), or hospital admission—with the implicit assumption that patients with a higher level of care have a higher severity of illness. Table 66-5 lists the patient-related attributes contributing to the RePEAT risk-adjustment score. As with the PRISA II score, analytic models including the RePEAT score have good calibration and discrimination with respect to predicting ED care and hospital admission. Furthermore, analytic models that compare costs and ED length of stay between EDs are improved by adjustment for severity of illness using the RePEAT score. These results demonstrate that RePEAT is a reasonable marker of severity of illness and that inclusion of this severity index substantially improves the ability to compare outcomes between EDs.

*Bibliography is available at Expert Consult.*
Bibliography


Institute of Medicine: To err is human: building a safer health care system, Washington, DC, 2000, National Academy Press.


International pediatric emergency medicine is an emerging academic field whose practitioners are committed to international collaboration aimed at improving the quality of care for children outside their national borders (Table 66-6).

Many models currently exist for the delivery of emergency care. The triage officer model is one in which a practitioner who works in an ED briefly provides intake for all patients and calls specialists to provide definitive care depending on the nature of the presenting complaint. The multiple physician model describes a scenario in which patients are divided by their chief complaints into medical, surgical, and pediatric groups. The field of emergency medicine provides a specialist skilled in the recognition, stabilization, and definitive treatment of a wide variety of acute illnesses and injuries. This approach to managing an emergency center is more efficient, relies less heavily on specialist availability, and requires fewer highly trained practitioners to operate. Children and adolescents constitute a subpopulation of emergency patients that deserves special attention because of pediatric-specific conditions, unique anatomy and physiology, developmental staging, and parental interactions.

The maturity of pediatric emergency medicine (PEM) in any given area depends on the healthcare priorities and resources of that geographic or physical setting. The places in which emergency care takes place range from the community (for those with no access to organized medical care) to state-of-the-art pediatric EDs in populated centers. The scope ranges from care of the individual patient to the management of populations of children involved in large-scale disasters. Barriers to quality care are different in each situation and in each part of the world, with the implication for the astute international PEM practitioner that solutions must be targeted to the local context of healthcare within a given environment.

**EMSC AND THE CONTINUUM OF CARE MODEL**

EMSC is a U.S. federal initiative designed to reduce child and youth disability and death as a result of severe illness or injury. The EMSC program has developed an operational framework for conceptualizing a systems approach to emergency care for children, known as the *continuum of care model*. The model specifically refers to the seamless care of ill and injured children from the community and medical home through to definitive care and return to the community. It has the following 5 principal components:

1. Prevention
2. Out-of-hospital care, both emergency response and prehospital transport
3. Hospital-based care: emergency center and inpatient unit
4. Interfacility transport, as necessary, for definitive or subspecialty care (see Chapter 66.1)
5. Rehabilitation

This framework can also be applied to discussion of emergency care for children on a global level. With medical infrastructures that may not be consistent or well-organized, or that have been weakened by civil strife, natural disasters, and economic loss, the focus of child health in the developing world has been on prevention and acute care.

**APPLYING THE CONTINUUM OF CARE MODEL TO THE DEVELOPING WORLD**

### Prevention

**Infectious Diseases**

International child health has focused mainly on reducing preventable childhood illnesses, primarily through immunizations. Enormous advances have been realized in measles, neonatal tetanus, and polio reduction; wild-type smallpox was eradicated in 1978. Although there are advocates for providing primary care interventions (e.g., vaccinations) in the ED, the role of the PEM practitioner in this area of prevention has been limited.

### Injuries

Injuries are a leading cause of childhood morbidity and mortality. Unintentional injuries constitute 90% of injury mortality to children ages 5–19 yr and are the cause of 9% of the world’s mortality. Intentional injuries, an underrecognized and underreported phenomenon primarily for cultural reasons, make a smaller but significant contribution. Unintentional injuries cause more than 2,000 childhood deaths daily or 950,000 annually worldwide. The burden of these deaths is borne disproportionately by children in middle- and lower-income countries.
countries, where more than 95% of all injury deaths occur. For each of these deaths, many more children are permanently disabled and an even larger number are treated and released without permanent sequelae.

The World Health Organization (WHO) and United Nations Children's Fund (UNICEF) have outlined several proven injury prevention strategies of which child health practitioners in the global community must be aware. The top 3 causes of injury mortality are traffic-related injuries, burns, and drowning. There are 7 specific effective strategies for reducing road traffic injuries: a minimum drinking age, appropriate child restraints and seatbelts, helmets for motorcycle and bicycle riders, reduced vehicle speeds around schools and residential areas, running lights on motorcycles, graduated licensing for drivers, and separation of different types of road users. There is insufficient evidence to demonstrate that school-based programs on drunk driving, increased pedestrian visibility, or designated driver programs are effective. Although these strategies have been proven effective, the data are based on research from the United States and may not be generalizable to other countries. It may be difficult to reduce vehicle speeds around schools when there is insufficient infrastructure for street signs. Alternatively, lack of separation of car and bus traffic from bicyclists and pedestrians contributes to unsafe and dangerous road conditions. This is more of a problem in lower- and middle-income countries, where bicycles and motorized 2-wheel vehicles are used to carry children as well as goods, while the drivers negotiate among rapidly moving vehicles. With rising income, these countries have seen increases in both the number of cars and the number of 2-wheeled vehicles, with a corresponding increase in the number of related injuries.

For reducing drowning deaths, strategies that have proven effective focus on creating barriers between children and water hazards, such as covering wells, buckets, and other standing sources of water, and placing high fences around pools (see Chapter 74). Burns have been addressed by advocating for installation of smoke detectors and lowering the temperature of water from water heaters (see Chapter 75). For the PEM practitioner, involvement in prevention depends largely on the local epidemiology of injuries and the factors contributing to those injuries. Involvement can include parental and patient education or activism to change local practices through laws and new community standards. Additionally, work can be done with groups of practitioners or healthcare centers to increase capacity to care for injured children. One can also work on a larger scale on projects initiated by a group such as the WHO, UNICEF, or Safe Kids Worldwide, to develop and evaluate intervention strategies that target specific preventable injuries.

Out-of-Hospital Care

Out-of-hospital care comprises access to emergency services,prehospital care, and interfacility transport of patients. Morbidity and mortality arise from delayed or limited access to emergency care, lack ofprehospital care, transport without proper monitoring or trained personnel, or delayed transport to a higher level of care. Safe transport of seriously ill children is a neglected global health issue. An emergency response system must address the following links in the patient's care: a communication system with prompt activation ofEMS, the correct assessment and initial treatment of the patient, and the rapid transport to definitive care.

Access to Care

When a child is injured or ill, a parent or caretaker must be able to access help and activate EMS. Many countries around the world have dedicated emergency numbers to rapidly dispatch medical, police, or fire services. The simple “112” emergency number has been adopted and is being phased in throughout the European Union member states, to be used to access medical, fire and police services in addition to secondary regional emergency access numbers. The universal U.S. emergency number system 911 today covers the large majority of the country (98%) and has enhanced features of automatically linking the phone number to an address. However, there remain limitations to universal access resulting from absence of phones in some households, unclear addresses in rural areas, and insufficient reach of the emergency system. In low- and middle-income countries, no such universal emergency numbers have been established, requiring access by direct dialing to an ambulance, if such private services exist. In most low- and middle-income countries, the family must bring the ill or injured child to the health facility for stabilization and treatment. For this to occur, families must overcome financial and geographic barriers, which can result in delayed presentation for care. This delay predictably increases the acuity of the illness or injury and associated complications, and decreases the likelihood of full recovery and survival.

Prehospital Care

In regions with maturing EMS systems, there must be adequately trained personnel to stabilize and transport the child to a medical facility. The quality and level of training of such prehospital personnel vary tremendously among countries and within regions of the same country. In urban areas, there is a greater concentration of medical care and therefore a greater opportunity to have strongprehospital training. In most of Asia and sub-Saharan Africa, trained personnel are used primarily to transfer patients between health facilities, and not from the initial site of illness or injury. In most high-income countries, EMS are dispatched to the patient.

A different approach to prehospital work is exemplified by the French EMS, called Service d'Aide Médicale Urgente (SAMU). In this system, a physician is integral to the prehospital team. A physician, typically an emergency medicine specialist in larger areas, will review every call for acuteness and can dispatch a physician-led team by ambulance to go to the patient’s home to assess, stabilize, and initiate treatment. This Franco-German system is used in other countries, including many in Latin America and Europe. There are no clear data on the cost-effectiveness and patient outcomes associated with delivery of patients to the nearest facility versus bringing hospital resources to the patient. Some research suggests, however, that it is difficult for ambulance-based physicians to maintain their field skills given the relatively low frequency of high-acuity or high-complexity cases.

Around the world, the effort to establish standardized approaches toprehospital care exists primarily in the form of courses to educate EMS and hospital personnel in the emergency management of patients. For trauma care, the WHO manuals Prehospital Trauma Care Systems and Guidelines for Essential Trauma Care both focus on guidelines for prehospital and trauma care systems that are affordable and sustainable. The AAP course Pediatric Education for Prehospital Professionals is a dynamic, modularized teaching tool designed to provide specific pediatrictprehospital education that can be adapted to any EMS system. Table 66-7 lists additionalprehospital resources.

Although most middle- and high-income countries have a system of trained EMS workers, low-income countries lack this advanced tier of emergency care. In these countries, commercial drivers, volunteers, and willing bystanders provide the first line of care. Training a cadre of first responders can rely on existing networks of aid or can be drawn from specific populations, such as students, soldiers, or public servants. Training needs to emphasize basic lifesaving and limb-saving interventions, including how to stop bleeding and support breathing, access advanced care, and splint broken limbs. In Ghana, for example, 335 taxi drivers participated in a first-aid course that relied heavily on demonstration and practice rather than knowledge transfer through didactic sessions. Taxi drivers were selected because they already provided much of the transport for injured patients, either voluntarily or for pay by the family. Two years after the course, external evaluators favorably rated the quality of their care in comparison with that of a group of untrained drivers. In rural areas, such first responders become vital in providing emergency interventions when more definitive care is distant. Thus, a system of trained first responders forms the foundation of an effectiveprehospital system.

Methods of Transport

In many low-income countries, there is no means of transport other than the family’s motorized or other type of transport. Health centers may only have 1 vehicle for transport to a higher-level facility. This
<table>
<thead>
<tr>
<th>Table 66-7</th>
<th>Pediatric Emergency Medicine (PEM) Resources</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prehospital</strong></td>
<td><strong>Advanced Medical Life Support (AMLS)</strong>&lt;br&gt;Newest course developed by the National Association of Emergency Medical Technicians (NAEMT) to provide more clinical teaching and reasoning around emergent medical problems. Course is open to physicians, nurses EMTs and paramedics.&lt;br&gt;Website: <a href="http://www.naemt.org/education/amls/amls.aspx">www.naemt.org/education/amls/amls.aspx</a></td>
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<tr>
<td></td>
<td><strong>Prehospital Trauma Life Support</strong>&lt;br&gt;Available in 33 countries, PHTLS is the leading continuing education program for prehospital emergency trauma care.&lt;br&gt;Website: <a href="http://www.phtls.org">www.phtls.org</a></td>
</tr>
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<td></td>
<td><strong>International Trauma Life Support</strong>&lt;br&gt;Training course for prehospital trauma care.&lt;br&gt;Website: <a href="http://www.itrauma.org">www.itrauma.org</a></td>
</tr>
<tr>
<td></td>
<td><strong>The Sphere Project</strong>&lt;br&gt;Downloadable modules on disaster preparedness.&lt;br&gt;Website: <a href="http://www.sphereproject.org">www.sphereproject.org</a></td>
</tr>
<tr>
<td></td>
<td><strong>Pediatric Education for Prehospital Professionals (PEPP)</strong>&lt;br&gt;Curriculum designed specifically to teach prehospital professionals how to assess and manage ill or injured children.&lt;br&gt;Website: <a href="http://www.peppsite.org">www.peppsite.org</a></td>
</tr>
<tr>
<td></td>
<td><strong>Pocket Book of Hospital Care for Children</strong>&lt;br&gt;A publication of WHO providing guidelines for the management of common illnesses with limited resources. Incorporates both the Emergency Triage Assessment and Treatment (ETAT) and Integrated Management of Childhood Illness (IMCI) guidelines.&lt;br&gt;Website: <a href="http://www.who.int/maternal_child_adolescent/documents/9241546700/en/index.html">www.who.int/maternal_child_adolescent/documents/9241546700/en/index.html</a></td>
</tr>
<tr>
<td><strong>Hospital care</strong></td>
<td><strong>Where There Is No Doctor: A Village Health Handbook</strong>&lt;br&gt;Healthcare manual for health workers, clinicians, and others involved in primary healthcare delivery and health promotion programs around the world. Available for purchase or as a free download.&lt;br&gt;Website: <a href="http://www.hesperian.org">www.hesperian.org</a></td>
</tr>
<tr>
<td></td>
<td><strong>CHILDisaster Network</strong>&lt;br&gt;Registry for those with education and experience in humanitarian emergencies to volunteer their time when needed in time of a disaster.&lt;br&gt;Website: <a href="http://www.aap.org/disaster">www.aap.org/disaster</a></td>
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<td></td>
<td><strong>Pocket Book of Hospital Care for Children</strong>&lt;br&gt;A publication of WHO providing guidelines for the management of common illnesses with limited resources. Incorporates both the Emergency Triage Assessment and Treatment (ETAT) and Integrated Management of Childhood Illness (IMCI) guidelines.&lt;br&gt;Website: <a href="http://www.who.int/maternal_child_adolescent/documents/9241546700/en/index.html">www.who.int/maternal_child_adolescent/documents/9241546700/en/index.html</a></td>
</tr>
<tr>
<td><strong>Access to academic publications relevant to PEM</strong></td>
<td><strong>HINARI Access to Research Initiative</strong>&lt;br&gt;Program established by WHO and others to enable developing countries to gain access to one of the world's largest collections of biomedical and health literature.&lt;br&gt;Website: <a href="http://www.who.int/hinari/en">www.who.int/hinari/en</a></td>
</tr>
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<td><strong>ACEP Ambassador Program</strong>&lt;br&gt;Provides the names of U.S.-boarded emergency medicine physicians who can provide advice and information on issues pertaining to the progress and status of emergency medicine in their assigned countries.&lt;br&gt;Website: <a href="http://www.acep.org/content.aspx?id=25138">www.acep.org/content.aspx?id=25138</a></td>
</tr>
<tr>
<td><strong>Involvement</strong></td>
<td><strong>International emergency medicine section, American College of Emergency Physicians</strong>&lt;br&gt;This group maintains a list of international organizations and clinical opportunities, many of which involve emergency care of children.&lt;br&gt;Website: <a href="http://www.acep.org/_InternationalSection/International-Emergency-Medicine-Related-Resources/">http://www.acep.org/_InternationalSection/International-Emergency-Medicine-Related-Resources/</a></td>
</tr>
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<td><strong>Section of International Child Health, American Academy of Pediatrics</strong>&lt;br&gt;Lists of non-U.S. clinical opportunities, many of which involve emergency care.&lt;br&gt;Website: <a href="http://www2.aap.org/sections/ich/working_oversseas.htm">http://www2.aap.org/sections/ich/working_oversseas.htm</a></td>
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<td></td>
<td><strong>WHO</strong>&lt;br&gt;Publication catalog, media resources, health articles, and current health news.&lt;br&gt;Website: <a href="http://www.who.int/topics/child_health/en">www.who.int/topics/child_health/en</a></td>
</tr>
<tr>
<td><strong>Health organizations involved in international PEM activities</strong></td>
<td><strong>UNICEF</strong>&lt;br&gt;Organization dedicated to providing lifesaving assistance to children affected by disasters and to protecting their rights in any circumstances.&lt;br&gt;Website: <a href="http://www.unicef.org">www.unicef.org</a></td>
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<tr>
<td></td>
<td><strong>Safe Kids Worldwide</strong>&lt;br&gt;The first and only international nonprofit organization dedicated solely to preventing unintentional childhood injury.&lt;br&gt;Website: <a href="http://www.safekids.org">www.safekids.org</a></td>
</tr>
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</table>
The emergency services in these centers are variable, but at least 1 pediatric-capable center, usually as part of an academic medical center. Anecdotally, most countries have developed at least 1 pediatric-specific emergency area (hydration and infusion rooms) can lessen the burden on inpatients. Children requiring emergency care frequently are not promptly recognized. Too often, children presenting to EDs are treated on a first-come first-served basis, in an approach that creates long waiting times for critically ill children, a contributor to unnecessary mortality. Medical facilities need to adopt an efficient and effective triage system in order to rapidly respond to the needs of patients and to assign the appropriate amount of resources. To this end, WHO has developed a course entitled Emergency Triage Assessment and Treatment (ETAT). This course teaches health practitioners to triage patients on arrival as having emergency, priority, or nonurgent signs and to provide emergency treatment for life-threatening conditions. ETAT emphasizes the evaluation of a patient’s ABCD status to identify emergency situations—the patency of the airway (A), the quality of breathing (B), the quality of circulation and presence of coma or convulsions (C), and the presence of severe dehydration (D).

One of the benefits of the ETAT guidelines is that they can be adapted to centers with limited resources and are applicable to areas with high morbidity and mortality from meningitis, dehydration, malaria, respiratory illness, and malnutrition. Another benefit is that the care algorithms are based on limited diagnostic studies, that is, hemoglobin measurement, blood smear for malaria, and bedside blood glucose testing. Widely accepted triage assessment guidelines are teachable to emergency care staff, and their adoption can provide better organization within a healthcare center. At the Queen Elizabeth Central Hospital in Blantyre, Malawi, for example, the institution of triage and rapid treatment in its emergency care center led to a 50% decrease in the mortality of children within 24 hr of presentation to the hospital, with a further 50% decrease as implementation and practice of triaging patients have continued.

Beyond triage, education on overall emergency center organization is a low-resource intervention that can obviate some of the obstacles to quality care delivery. Additionally, the arrangement of short-stay areas (hydration and infusion rooms) can lessen the burden on inpatient units.

Pediatric-Specific Emergency Centers
Descriptions on the development of pediatric-specific emergency centers are insufficient. Anecdotally, most countries have developed at least 1 pediatric-capable center, usually as part of an academic medical center. The emergency services in these centers are variable, but certainly can be a starting point from which to build overall improvement in pediatric emergency care.

Practitioners
Throughout the world, nurses, paramedics, and nonspecialist physicians provide most of the care to acutely ill or injured children. The majority of sick children attend local clinics or district or central hospitals, where financial and human resources are not always matched to the potential acuity of presenting patient complaints. Nominal supervision is provided to staff attending these patients. Pediatric EDs located in tertiary hospitals are often staffed by training physicians with little or no supervision from faculty, who themselves may have limited exposure to or training in PEM. General hospitals lack dedicated pediatric staff; guidelines as to which patients should be moved to a higher level of care are often not standardized and depend on local influences and/or cultural beliefs about health and illness.

Clinical Guidelines
The Integrated Management of Childhood Illnesses (IMCI) guidelines were developed by the WHO and UNICEF to provide assistance in the initial triage and management of the presenting signs and symptoms of the major killers of the under–5 yr population in first-level health facilities (e.g., clinics, health centers, and outpatient departments of hospitals). The flow charts within each chapter of the IMCI manuals allow easy accessibility to materials that can enhance education and outreach to less experienced health workers.

Evaluations in various countries of the implementation of IMCI guidelines have shown improvements in health worker performance and quality of care as well as decreases in delay in treatment and mortality of under–5 yr children. These guidelines also dramatically reduce the cost of healthcare. The WHO website provides all the necessary implementation tools, including course manuals and evaluation tools.

Trauma
Morbidity and mortality from trauma is one of the most prevalent problems for children worldwide. Trauma care presents the challenge of sequential, often simple, interventions that must be performed in a timely manner to limit the severity of the outcome. However, with lack of specific training, signs and symptoms of pediatric trauma may go unrecognized or may be underappreciated. Trauma courses such as Advanced Trauma Life Support are educational tools that can be disseminated to improve the quality of care at emergency centers worldwide. For low-resource settings, the WHO has developed the Integrated Management for Emergency and Essential Surgical Care toolkit, which provides clear directions and reasoning for the initial care of injured patients. Not expressly addressed in the Advanced Trauma Life Support course is specific concern about child abuse as the cause of trauma. This is an area of pediatric care that many countries do not yet address in their medical training, their law enforcement, or their judicial systems. The epidemiologic need for reliable trauma registries is great, as is the need to identify personnel with trauma management skill sets and dedicated trauma centers to serve as higher-level referral sites.

Equipment
Pediatric emergency textbooks, pediatric and emergency medicine professional organizations, WHO, and nongovernmental and governmental health organizations have all published pediatric emergency equipment guidelines, for a variety of settings in which acutely ill and injured children would present. Although these equipment guidelines may represent minimum supplies to treat the widest variety of pediatric emergencies, the roles of substitution and improvisation often provide for equivalent function of recommended supplies.

Inpatient Services
After the initial stabilization, children requiring ongoing care are admitted to the hospital. The quality of inpatient services varies greatly depending on institutional and provider experience, comfort with pediatric conditions, and the resources available to treat them. The WHO has produced the Pocket Book of Hospital Care for Children,
which is based on IMCI guidelines and focuses on inpatient management of high-morbidity/high-mortality illnesses common in developing countries.

**HUMANITARIAN DISASTERS**

Children are a vulnerable population who experience disproportionate suffering during humanitarian emergencies, either natural (earthquakes, tsunamis, hurricanes, floods, and droughts) or manmade (armed conflicts, terrorist attacks). The under–5 yr population is especially susceptible to infectious diseases, malnutrition, and trauma following disasters. The Rainbow Center for Global Child Health at the Case Western Reserve University School of Medicine offers a training course, Management of Humanitarian Emergencies: Focus on Children and Families, that concentrates on the needs of children in disasters. The intent of the Center is to educate and train health professionals, relief workers, and policymakers to recognize and address the unique needs of children affected by manmade and natural disasters worldwide. The AAP also maintains a CHILDisaster Network, which acts as an electronic database of child health professionals with education and experience in humanitarian emergencies. Nongovernmental organizations can access the database to solicit practitioners to aid in disaster response.

The WHO’s *Manual for the Health Care of Children in Humanitarian Emergencies* is based on IMCI guidelines and addresses the emergency care of children in disaster situations in which hospital facilities and resources are not immediately available. It goes beyond the IMCI guidelines by discussing initial assessment and management of trauma, burns, and poisonings. Preexisting IMCI guidelines assumed a functioning health system that facilitated the referral of children, which may not be available in all emergency situations. This manual also includes the initial management of severe conditions, such as injuries, burns, neonatal illness, and psychosocial problems, which are considered high priority in acute care settings.

**Exchange and Dissemination of Information**

The WHO established the HINARI (Health InterNetwork Access to Research Initiative) program to allow free or reduced-cost access to more than 6,200 journal publications. This Internet access is made available to the 108 countries with gross national income per capita less than $3,500. For middle-income countries not meeting the financial eligibility, Internet access continues to be a barrier, and resources may be limited to out-of-date textbooks and journals.

Another valuable tool is the website Pemdatabase.org. This nonproprietary site was started as an online resource for PEM practitioners. It contains links to PEM abstracts and articles, evidence-based reviews, pediatric resuscitation websites, relevant journals, as well as PEM conferences and professional organizations.

*Bibliography is available at Expert Consult.*
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Bibliography
Injuries are the leading cause of death in American children and young adults and are responsible for more childhood deaths than all other causes combined (see Chapter 5.1). Children are particularly vulnerable to injury for a number of reasons, including their small size, relative physical uncoordination, and limited ability to predict or understand danger. In addition, the immaturity of their developing bones, ligaments, and muscles; their thin body walls; and their relatively large heads, compared with total body surface area, make young children susceptible to serious or fatal injury from falls and collisions.

Most injuries in childhood are unintentional, and many are preventable. Motor vehicle–related injuries are the most common cause of unintentional injury and death for U.S. children, many of which are related to speeding, aggressive driving, failure to use proper passenger restraints, and/or alcohol. Consistent use of bicycle helmets could reduce the severity of head injuries, the leading cause of death when a bicyclist is struck by a car, by more than 80%. Four-sided fencing around swimming pools and use of flotation devices for every passenger in a boat could greatly reduce the risk of drowning, the second leading cause of accidental death in children younger than 5 yr and the third major cause of death in adolescents. Serious injuries can become fatal when appropriate medical care is delayed.

Rapid, effective bystander cardiopulmonary resuscitation (CPR) for children is associated with survival rates as high as 70%, with good neurologic outcome. However, bystander CPR is still provided for less than 50% of children who experience cardiac arrest outside medical settings. This has led to long-term survival rates of <40%, with many survivors suffering a poor neurologic outcome.

**APPROACH TO THE EMERGENCY EVALUATION OF A CHILD**

The first response to a pediatric emergency of any cause is a systematic, rapid general assessment of the scene and the child to identify immediate threats to the child, care providers, or others. If an emergency is identified, the emergency response system (emergency medical services [EMS]) should be activated immediately. Care providers should then proceed through primary, secondary, and tertiary assessments as allowed by the child's condition, safety of the scene, and resources available. This standardized approach provides organization to what might otherwise be a confusing or chaotic situation and reinforces an organized thought process for care providers. If, at any point in these assessments, the caregiver identifies a life-threatening problem, the assessment is halted and lifesaving interventions are begun. Further assessment and intervention should be delayed until other caregivers arrive or the condition is successfully treated.

**General Assessment**

Upon arrival at the scene of a compromised child, a caregiver's first task is a quick survey of the scene itself. Is the rescuer or child in imminent danger because of circumstances at the scene (fire, high-voltage electricity)? If so, can the child be safely extricated to a safe location for assessment and treatment? Can the child be safely moved with the appropriate precautions (i.e., cervical spine protection), if indicated? A rescuer is expected to proceed only if these safety conditions have been met.

Once the caregiver and patient's safety has been ensured, the caregiver performs a rapid visual survey of the child, assessing the child's general appearance and cardiopulmonary function. This action should be very quick (only a few seconds) and should include assessment of (1) general appearance (determining color, tone, alertness, and responsiveness); (2) adequacy of breathing (distinguishing between normal, comfortable respirations and respiratory distress or apnea); and (3) adequacy of circulation (identifying cyanosis, pallor, or mottling). A child found unresponsive from an unwitnessed collapse should be approached with a gentle touch and the verbal question, “Are you OK?” If there is no response, the caregiver should immediately shout for help and send someone to both activate the emergency response system (EMS) and locate an automated external defibrillator (AED) (Fig. 67-1). The provider should then determine whether the child is breathing and, if not, provide 2 rescue breaths as described later under “Recognition and Treatment of Respiratory Distress and Failure.” If the child is adequately breathing, then the circulation is quickly assessed. Any child with a heart rate below 60 beats/min or without a pulse requires immediate CPR, as described under...
"Recognition and Management of Cardiac Arrest." If the caregiver witnesses the sudden collapse of a child, the caregiver should have a higher suspicion for a sudden cardiac event. In this case, rapid deployment of an AED is of paramount importance. The provider should very briefly delay care of the child to activate EMS and locate the nearest AED.

Primary Assessment

Once the emergency response system has been activated and the child is determined not to need CPR, the caregiver should proceed with a primary assessment that includes a brief, hands-on assessment of cardiopulmonary and neurologic function and stability. This assessment includes a limited physical exam, evaluation of vital signs, and measurement of pulse oximetry if possible. Again, a standardized approach is best. The American Heart Association, in its Pediatric Advanced Life Support (PALS) curriculum, supports the structured format of **Airway, Breathing, Circulation, Disability, Exposure (ABCDE)**. The goal of the primary assessment is to obtain a focused, systems-based assessment of the child’s injuries or abnormalities, so that resuscitative efforts can be directed to these areas; if the caregiver identifies a life-threatening abnormality, further evaluation is postponed until appropriate corrective action has been taken.

The exam and vital sign data can be interpreted only if the caregiver has a thorough understanding of normal values. In pediatrics, normal respiratory rate, heart rate, and blood pressure have age-specific norms (Table 67-1). These ranges can be difficult to remember, especially if used infrequently. However, several standard principals apply: (1) no child’s respiratory rate should be >60 breaths/min for a sustained period; (2) normal heart rate is roughly 2-3 times normal respiratory rate for age; and (3) a simple guide for pediatric blood pressure is that...
Normal Vital Signs According to Age

<table>
<thead>
<tr>
<th>AGE</th>
<th>HEART RATE (beats/min)</th>
<th>BLOOD PRESSURE (mm Hg)</th>
<th>RESPIRATORY RATE (breaths/min)</th>
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<tbody>
<tr>
<td>Premature</td>
<td>120-170*</td>
<td>55-75/35-45†</td>
<td>40-70*</td>
</tr>
<tr>
<td>0-3 mo</td>
<td>100-150*</td>
<td>65-85/45-55</td>
<td>35-55</td>
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<tr>
<td>3-6 mo</td>
<td>90-120</td>
<td>70-90/50-65</td>
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<td>6-12 mo</td>
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<td>95-110/60-75</td>
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<td>55-85</td>
<td>110-135/65-85</td>
<td>12-18</td>
</tr>
</tbody>
</table>

*In sleep, infant heart rates may drop significantly lower, but if perfusion is maintained, no intervention is required.
†A blood pressure cuff should cover approximately two-thirds of the arm; too small a cuff yields spuriously high pressure readings, and too large a cuff yields spuriously low pressure readings.
‡Many premature infants require mechanical ventilatory support, making their spontaneous respiratory rate less relevant.

Airway and Breathing

The most common precipitating event for cardiac instability in infants and children is respiratory insufficiency. Therefore, rapid assessment of respiratory failure and immediate restoration of adequate ventilation and oxygenation remain the first priority in the resuscitation of a child. Using a systematic approach, the caregiver should first assess whether the child’s airway is patent and maintainable. A healthy, patent airway is open and unobstructed, allowing normal respiration without noise or effort. A maintainable airway is one that is either already patent or can be made patent with a simple maneuver. To assess airway patency, the provider should look for breathing movements in the child’s chest and abdomen, listen for breath sounds, and feel the movement of air at the child’s mouth and nose. Abnormal breathing sounds (i.e., snoring or stridor), increased work of breathing, and apnea are all findings potentially consistent with airway obstruction. If there is evidence of airway obstruction, then maneuvers to relieve the obstruction should be instituted before the caregiver proceeds to evaluate the child’s breathing (see under “Recognition and Treatment of Respiratory Distress and Failure”).

Assessment of breathing includes evaluation of the child’s respiratory rate, respiratory effort, abnormal sounds, and pulse oximetry. Normal breathing appears comfortable, is quiet, and occurs at an appropriate rate. Abnormal respiratory rates include apnea and rates that are either too slow (bradypnea) or too fast (tachypnea). Bradypnea and irregular respiratory patterns require urgent attention, as they are often signs of impending respiratory failure and apnea. Signs of increased respiratory effort include nasal flaring, grunting, chest or neck muscle retractions, head bobbing, and “seesaw” respirations. Hemoglobin oxygen desaturation, as measured by pulse oximetry, often accompanies parenchymal lung disease apnea or airway obstruction. However, providers should keep in mind that adequate perfusion is required to produce a reliable oxygen saturation measurement. A child with low oxygen saturation is a child in distress. Central cyanosis is a sign of severe hypoxia and indicates an emergent need for oxygen supplementation and respiratory support.

Circulation

Cardiovascular function is assessed by evaluation of skin color and temperature, heart rate, heart rhythm, pulses, capillary refill time, and blood pressure. In nonhospital settings, much of the important information can be obtained without measuring the blood pressure; lack of blood pressure data should not prevent the provider for determining adequacy of circulation or implementing a lifesaving response. Mottling, pallor, delayed capillary refill, cyanosis, poor pulses, and cool extremities are all signs of diminished perfusion and compromised cardiac output. Tachycardia is the earliest and most reliable sign of shock, but it is itself fairly nonspecific and should be correlated with other components of the exam, such as weakness, threadiness, and absence of pulses. An age-specific approach to pulse assessment will yield best results.

Disability

In the setting of a pediatric emergency, disability refers to a child’s neurologic function in terms of the level of consciousness and cortical function. Standard evaluation of a child’s neurologic condition can be done quickly with an assessment of pupillary response to light (if one is available) and use of either of the standard scores used in pediatrics: the Alert, Verbal, Pain, Unresponsive (AVPU) Pediatric Response Scale and the Glasgow Coma Scale (GCS) (Tables 67-2, 67-3, and 68-1). The causes of decreased level of consciousness in children are numerous and include conditions as diverse as respiratory failure with hypoxia or hypercarbia, hypoglycemia, poisonings or drug overdose, trauma, seizures, infection, and shock. Most commonly, an ill or injured child has an altered level of consciousness because of respiratory compromise, circulatory compromise, or both. Any child with a depressed

level of consciousness should be immediately assessed for abnormaliti- 
ies in cardiorespiratory status.

**The Alert, Verbal, Pain, Unresponsive Pediatric Response Scale.** The AVPU scoring system is used to determine both a child’s level of consciousness and cerebral cortex function. Unlike the GCS (see later), the AVPU scale is not developmentally dependent—a child does not have to understand spoken language or follow commands, merely respond to a stimulus. The child is scored according to the amount of stimulus required to get a response, from alert (no stimulus, the child is already awake and interactive) to unresponsive (child does not respond to any stimulus) (see Table 67-2).

The Glasgow Coma Scale. Although the GCS has not been validated as a prognostic scoring system for infants and young children as it has been in adults, it is commonly used in the assessment of pediatric patients with an altered level of consciousness. The GCS is the most widely used method of evaluating a child’s neurologic function and has 3 components. Individual scores for eye opening, verbal response, and motor response are added together, with a maximum of 15 points (see Table 67-3). Patients with a GCS score ≤8 require aggres- sive management, including stabilization of the airway and breathing with endotracheal intubation and mechanical ventilation, respectively, and, if indicated, placement of an intracranial pressure monitoring device. The Full Outline of Unresponsiveness (FOUR) score is another useful assessment and monitoring tool (see Table 68-1).

**Exposure**

Exposure is the final component of the pediatric primary assessment. This component of the exam is reached only after the child’s airway, breathing, and circulation have been assessed and determined to be stable or have been stabilized through simple interventions. In this setting, exposure stands for the dual responsibility of the provider to both expose the child to assess for previously unidentified injuries and consider prolonged exposure in a cold environment as a possible cause of hypothermia and cardiopulmonary instability. The provider should undress the child (as is feasible and reasonable) to perform a focused physical exam, assessing for burns, bruising, bleeding, joint laxity, and fractures. If possible, the provider should assess the child’s temperature. All maneuvers should be performed with careful maintenance of cervical spine precautions.

**Secondary Assessment**

For care providers in community or outpatient settings, transfer of care of a child to emergency or hospital personnel may occur before a full secondary assessment is possible. However, before the child is removed from the scene and separated from witnesses or family, a brief history should be obtained for medical providers at the accepting facility. The components of a secondary assessment include a focused history and focused physical exam.

The history should be targeted to information that could explain cardiorespiratory or neurologic dysfunction and should take the form of a SAMPLE history (Signs/symptoms, Allergies, Medications, Past medical history, timing of Last meal, and Events leading to this situ- ation). Medical personnel not engaged in resuscitative efforts can be dispatched to elicit history from witnesses or relatives. The physical exam during the secondary assessment is a thorough head-to-toe exam, although the severity of the child’s illness or injury could necessitate curtailing portions of the exam or postponing nonessential elements until a later time.

**Tertiary Assessment**

The tertiary assessment occurs in a hospital setting, where ancillary laboratory and radiographic assessments contribute to a thorough understanding of the child’s condition. A basic blood chemistry profile, complete blood count, liver function tests, coagulation studies, and arterial blood gas analyses give fairly broad (but somewhat nonspec- ific) estimates of renal function, acid–base balance, cardiorespiratory function, and presence or absence of shock. Chest radiographs can be useful to evaluate both the heart and lungs, although more detailed estimates of heart function and cardiac output can be made with echocardiography. Arterial and central venous catheters can be placed to monitor arterial and central venous pressure (see under “Vascular Access”).

**RECOGNITION AND TREATMENT OF RESPIRATORY DISTRESS AND FAILURE**

The goals of initial management of respiratory distress or failure are to rapidly stabilize the child’s airway and breathing and to identify the cause of the problem so that further therapeutic efforts can be appro- priately directed.

**Airway Obstruction**

Children <5 yr old are particularly susceptible to foreign-body aspira- tion and choking. Liquids are the most common cause of choking in infants, whereas small objects and food (e.g., grapes, nuts, hot dogs, candies) are the most common source of foreign bodies in the airways of toddlers and older children. A history consistent with foreign-body aspiration is considered diagnostic. Any child in the proper setting with the sudden onset of choking, stridor, or wheezing has foreign-body aspiration until proven otherwise.

Airway obstruction is treated with a sequential approach, starting with the head-tilt/chin-lift maneuver to open and support the airway, followed by inspection for a foreign body, and, if possible and reasonable, suctioning or if one is visualized (Fig. 67-2). Blind suctioning or finger sweeps of the mouth are not recommended. A nasopharyngeal airway or oropharyngeal airway can be inserted for airway support, if indi- cated. A conscious child suspected of having a partial foreign-body obstruction should be permitted to cough spontaneously until coughing is no longer effective, respiratory distress and stridor increase, or the child becomes unconscious.

If the child becomes unconscious, the child should be gently placed on the ground, supine. The provider should then open the airway with the head-tilt/chin-lift maneuver and attempt mouth-to-mouth ventilation (Figs. 67-3 and 67-4). If ventilation is unsuccessful, the airway is repositioned, and ventilation attempted again. If there is still no chest rise, attempts to remove a foreign body are indicated. In an infant <1 yr old, a combination of 5 back blows and 5 chest thrusts is administered.

**Figure 67-2** Opening the airway with the head-tilt/chin-lift maneuver. One hand is used to tilt the head, extending the neck. The index finger of the rescuer’s other hand lifts the mandible outward by lifting the chin. Head-tilt should not be performed if a cervical spine injury is suspected. (From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Sub- committees, American Heart Association. Part V. Pediatric basic life support, JAMA 268:2251–2261, 1992.)
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(Fig. 67-5). After each cycle of back blows and chest thrusts, the child’s mouth should be visually inspected for the presence of the foreign body. If identified within finger’s reach, it should be removed with a gentle finger sweep. If no foreign body is visual, ventilation is again attempted. If this is unsuccessful, the head is repositioned, and ventilation attempted again. If there is no chest rise, the series of back blows and chest thrusts is repeated.

For a conscious child >1 yr old, providers should give a series of 5 abdominal thrusts (Heimlich maneuver) with the child standing or sitting (Fig. 67-6); this should occur with the child lying down if unconscious (Fig. 67-7). After the abdominal thrusts, the airway is examined for a foreign body, which should be removed if visualized. If no foreign body is seen, the head is repositioned, and ventilation attempted. If it is unsuccessful, the head is repositioned and ventilation is attempted again. If these efforts are unsuccessful, the Heimlich sequence is repeated.

(Fig. 67-6) Abdominal thrusts with the victim standing or sitting (conscious). (From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part V. Pediatric basic life support, JAMA 268:2251–2261, 1992.)

(Fig. 67-5) Back blows (top) and chest thrusts (bottom) to relieve foreign-body airway obstruction in the infant. (From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part V. Pediatric basic life support, JAMA 268:2251–2261, 1992.)
Airway Narrowing

Airway obstruction can also be caused by airway narrowing, in both the upper and lower airways. Upper airway obstruction refers to narrowing of the extrathoracic portion of the airway, including the oropharynx, larynx, and trachea. In the upper airways, narrowing is most often caused by airway edema (croup or anaphylaxis). Lower airway disease affects all intrathoracic airways, notably the bronchi and bronchioles. In the lower airways, bronchiolitis and acute asthma exacerbations are the major contributors to intrathoracic airway obstruction in children, causing airway narrowing through a combination of airway swelling, mucus production, and circumferential smooth muscle constriction of smaller airways.

Airway support for these processes is dictated by both the underlying condition and the clinical severity of the problem. In cases of mild upper airway obstruction, the child has minimally elevated work of breathing (evidenced by tachypnea and few to mild retractions). Stridor, if present at all, should be audible with only coughing or activity. Children with these findings can be supported with nebulized cool mist and supplemental oxygen as needed. In cases with moderate obstruction, in which the child has a higher work of breathing and more pronounced stridor, nebulized racemic epinephrine and oral or intravenous (IV) dexamethasone can be added. Children with severe upper airway obstruction have marked retractions, prominent stridor, and decreased air entry on auscultation of the lung fields. Most children with significant airway obstruction are also hypoxic, and many appear dyspneic and agitated. A child in severe distress needs to be closely observed, as the signs of impending respiratory failure may be initially confused with improvement. Stridor becomes quieter and retractions less prominent when a child’s respiratory effort begins to diminish. The child in respiratory failure can be distinguished from one who is improving by evidence of poor air movement on auscultation and lethargy or decreased level of consciousness from hypercarbia, hypoxia, or both. When anaphylaxis is suspected as the cause for upper airway edema, providers should administer an intramuscular or IV dose of epinephrine as needed (see Chapter 149). No matter the cause, any child in impending respiratory failure should be prepared for endotracheal intubation and respiratory support.

In cases of lower airway obstruction, therapies are targeted to both relieving the obstruction and reducing the child’s work of breathing. Inhaled bronchodilators, such as albuterol, augmented by oral or IV corticosteroids, remain the mainstay of therapy in settings of mild to moderate acute distress caused by lower airway obstruction. Children with more significant obstruction appear dyspneic, with tachypnea, retractions, and easily audible wheezing. In these cases, the addition of an anticholinergic agent, such as nebulized ipratropium bromide, or a smooth muscle relaxant, such as magnesium sulfate, may provide further relief, although the evidence for these measures remains controversial (see Chapter 144). Supplemental oxygen and IV fluid hydration can also be useful adjuncts. As in cases of upper airway obstruction, impending respiratory failure in children with lower airway obstruction can be insidious. When diagnosed early in a school-age child who is cooperative, respiratory failure can be averted through judicious use of noninvasive support, with continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), or heliox (combined helium-oxygen therapy). Endotracheal intubation should be performed only by skilled providers, preferably in a hospital setting, because there is a high risk of respiratory and circulatory compromise in patients with lower airway obstruction during the procedure.

Parenchymal Lung Disease

Parenchymal lung disease includes a heterogeneous list of conditions, such as pneumonia, acute respiratory distress syndrome, pneumonitis, bronchiolitis, bronchopulmonary dysplasia, cystic fibrosis, and pulmonary edema. The commonalities of these conditions are their effects on the small airways and alveoli, including inflammation and exudation leading to consolidation of lung tissue, decreased gas exchange, and increased work of breathing. Clinical management of these conditions includes specific treatment as indicated (i.e., antibiotics for bacterial pneumonia) and supportive care in the form of supplemental oxygen, noninvasive respiratory support (with CPAP or BiPAP), or invasive mechanical ventilation.

Advanced Airway Management Techniques

Bag-Valve-Mask Positive Pressure Ventilation

Rescue breathing with a bag-valve-mask apparatus can be as effective as endotracheal intubation and safer when the provider is inexperienced with intubation. Bag-valve-mask ventilation itself requires training to ensure that the provider is competent to select the correct mask size, open the child’s airway, form a tight seal between the mask and the child’s face, deliver effective ventilation, and assess the effectiveness of the ventilation. An appropriately sized mask is one that fits over the child’s mouth and nose but does not extend below the chin or over the eyes (Fig. 67-8). An adequate seal is best achieved via a combination “C–E” grip on the mask, in which the thumb and index finger form the letter “C” on top of the mask, pressing the mask downward onto the child’s face, and the remaining 3 fingers form an “E” grip under the child’s mandible, holding the jaw forward and extending the head up toward the mask. Using this method, the care provider can secure the mask to the child’s face with 1 hand and use the other hand to compress the ventilation bag (Fig. 67-9).

The provider may have to move the head and neck through a range of positions to find the one that best maintains airway patency and allows maximal ventilation. In infants and young children, optimal ventilation is often provided when the child’s head is in the neutral “sniffing” position without hyperextension of the head (Fig. 67-10). Poor chest rise and persistently low oxygen saturation values indicate inadequate ventilation. In this setting, the care provider should recheck the mask’s seal on the child’s face, reposition the child’s head, and consider suctioning the airway if indicated. If these maneuvers do not restore ventilation, then the provider should consider endotracheal intubation.

Endotracheal Intubation

A child requires intubation when at least 1 of these conditions exists: (1) the child is unable to maintain airway patency or protect the airway against aspiration (as occurs in settings of neurologic compromise); (2) the child is failing to maintain adequate oxygenation; (3) the child is failing to control blood carbon dioxide levels and maintain safe
situation is an emergency (i.e., apnea, asystole, unresponsiveness) and the administration of drugs would cause an unacceptable delay. Because many intubations in critically ill children are emergency procedures, caregivers should be prepared for rapid sequence intubation (RSI) (Fig. 67-11; Table 67-4). The goals of RSI are to induce anesthesia and paralysis and to complete intubation quickly. This approach minimizes elevations of intracranial pressure and blood pressure that may accompany intubation in awake or lightly sedated patients. Because the stomach generally cannot be emptied before RSI, the Sellick maneuver (downward pressure on the cricoid cartilage to compress the esophagus against the vertebral column) should be used to prevent aspiration of gastric contents.

Once the patient is intubated, proper ET placement should be assessed by auscultation of breath sounds, evidence of symmetric chest rise, and analysis of exhaled carbon dioxide (CO2) by a colorimetric device placed within the respiratory tubing near the ET or a device that directly measures carbon dioxide elimination (i.e., capnogram or capnograph). Chest radiography is necessary to confirm appropriate tube position.

**RECOGNITION AND MANAGEMENT OF SHOCK**

In simple terms, shock occurs when oxygen and nutrient delivery to the tissues is inadequate to meet metabolic demands (see Chapter 70).
flow to the body, as occurs when a ductus arteriosus closes in a child with ductus-dependent systemic blood flow in pericardial tamponade, tension pneumothorax, or massive pulmonary embolism.

The evaluation of a child in shock should proceed as described in the preceding sections on primary, secondary, and tertiary assessments. If the child presents in a hospital setting, providers should obtain central venous and arterial access to permit a more thorough laboratory assessment of all organ systems, including studies of renal and liver function, acid–base balance and presence of lactic acidosis, hypoxemia and/or hypercapnia, and evidence of coagulopathy or disseminated intravascular coagulation. Chest radiography and more sophisticated assessments, such as echocardiography, may also be useful. Respiratory and cardiovascular support should be provided as indicated.

The treatment of shock focuses on the modifiable determinants of oxygen delivery while reducing the imbalance between oxygen demand and supply. A multipronged approach is recommended; it consists of optimizing the oxygen content of the blood, improving the volume and distribution of cardiac output, correcting metabolic derangements, and reducing oxygen demand. Blood oxygen content is maximized when hemoglobin values are normal and 100% of available hemoglobin is saturated with oxygen. Transfusion should be considered in the presence of hemorrhagic or distributive shock, in which crystalloid volume resuscitation has led to hemodilution and anemia. High oxygen saturations may be achieved by simple maneuvers such as oxygen administration via nasal cannula or face mask, but supportive measures that provide positive pressure, such as CPAP, BiPAP, or even mechanical ventilation, may be necessary. Therapies to increase cardiac output should be selected on the basis of underlying pathophysiology. For hypovolemic and distributive shock, aggressive volume resuscitation, guided by arterial and central venous pressures, is the mainstay of therapy. In obstructive shock, relief of the obstruction is critical. The ductus arteriosus can often be reopened with prostaglandin administration, and tamponade physiology can be relieved with appropriate drain placement, as described under “Nonvascular Emergency Procedures.”

**RECOGNITION OF BRADYARRHYTHMIAS AND TACHYARRHYTHMIAS**

In the advanced life support setting, arrhythmias are most usefully classified according to the observed heart rate (slow or fast) and its effect on perfusion (adequate or poor). If, in the primary survey, a caregiver finds a child with an abnormal heart rate plus poor perfusion and/or altered mental status, then the rhythm is inadequate no matter its rate. In those settings, the child is diagnosed with shock, and further evaluation is halted until appropriate resuscitation has been initiated.

**Bradyarrhythmias**

By definition, a child is bradycardic when the heart rate is slower than the normal range for age (see Table 67-1). Sinus bradycardia can be a harmless incidental finding in an otherwise healthy person and is not commonly associated with cardiac compromise. A relative bradycardia occurs when the heart rate is too slow for a child’s activity level or metabolic needs. A clinically significant bradycardia occurs when the heart rate is slow and there are signs of systemic hypoperfusion (i.e., pallor, altered mental status, hypotension, acidosis). Symptomatic bradycardia occurs most often in the setting of hypoxia but can also be caused by hypoglycemia, hypocalcemia, other electrolyte abnormalities, and intracranial hypertension. Bradyarrhythmias are often the most common prearrest rhythms in young children.

Initial management of symptomatic bradycardia includes support or opening of the airway and confirming or establishing adequate oxygenation and ventilation (Fig. 67-12). After the child’s breathing has been secured, the child should be reassessed for continued bradycardia and poor perfusion. If cardiac compromise was solely the result of respiratory insufficiency, support of the child’s airway and breathing may have been sufficient to restore normal hemodynamics. If respiratory support does not correct the perfusion abnormalities, then further care is based on the quality of perfusion and the degree of

The definition of shock does not include hypotension, and it is important for care providers to understand that shock does not begin when blood pressure drops; it merely worsens and becomes more difficult to treat once blood pressure is abnormal.

Early compensated shock, whereby oxygen delivery is mostly preserved through compensatory mechanisms, is defined by the presence of normal blood pressure. When compensatory mechanisms fail, the shock progresses to decompensated shock, which is defined by hypotension and organ dysfunction. In irreversible shock, organ failure progresses and death ensues.

Shock is also often described according to the underlying pathophysiology, which dictates the appropriate therapeutic response. Hypovolemic shock is the most common type of shock in children worldwide, usually related to fluid losses from severe diarrhea. Hemorrhage is a cause of hypovolemic shock after trauma or intestinal hemorrhage. When hypovolemia occurs as a result of third spacing of intravascular fluids into the extravascular compartment, the shock is described as distributive shock. The most common causes of distributive shock are sepsis and burn injuries, in which release of inflammatory cytokines causes massive capillary leak of fluid and proteins, leading to low oncotic pressure and intravascular volume. In settings of profound myocardial dysfunction, a child has tissue hypoperfusion from cardiacogenic shock. The most common causes of cardiogenic shock are congenital heart disease, myocarditis, and cardiomyopathies. Obstructive shock occurs when cardiac output is lowered by obstruction of blood
bradycardia. A heart rate less than 60 beats/min with poor perfusion is an indication to begin chest compressions. If the bradycardia persists, vascular access should be obtained; resuscitative epinephrine should be administered, and it should be repeated every 3-5 min for persistent symptomatic bradycardia. If increased vagal tone (e.g., in the setting of head injury with raised intracranial pressure) or primary atrioventricular block is suspected, atropine can also be given. For cases of refractory bradycardia, cardiac pacing should be considered. During the resuscitation of a child with bradycardia, providers should assess and treat factors known to cause bradycardia, referred to collectively as the 6 Hs (hypoxia, hypovolemia, hydrogen ions [acidosis], hypokalemia or hyperkalemia, hypoglycemia, hypothermia), and 5 Ts (toxins, tamponade, tension pneumothorax, thrombosis [in either the pulmonary or cardiac circulations], and trauma [causing hypovolemia, intracranial hypertension, cardiac compromise or tamponade]) (Table 67-5).

Tachyarrhythmias
Tachyarrhythmias represent a variety of rhythm disturbances of both atrial and ventricular origin (see Chapter 435). Sinus tachycardia is a normal physiologic response to the body’s need for increased cardiac output or oxygen delivery, as occurs with fever, exercise, or stress. It can also occur in more pathologic states, such as hypovolemia, anemia, pain, anxiety, and metabolic stress. Tachyarrhythmias that do not originate in the sinus node are often categorized as narrow complex rhythms (those originating in the atrium, such as atrial flutter or supraventricular tachycardia [SVT]) and wide complex rhythms (those rhythms of ventricular origin, such as ventricular tachycardia).

The initial management of tachycardia includes confirmation that the child has an adequate airway and life-sustaining breathing and circulation (Fig. 67-13). For children with persistent symptoms, further treatment is based on whether the QRS complex of the electrocardiogram (ECG) is narrow (≤0.09 sec) or wide (>0.09 sec). For narrow complex tachycardia, providers must distinguish between sinus tachycardia and SVT. In sinus tachycardia, (a) the history and onset are consistent with a known cause of tachycardia, such as fever or dehydration and (b) P waves are consistently present, are of normal morphology, and occur at a rate that varies somewhat. In SVT, (a) onset is often abrupt without prodrome and (b) P waves are absent or polymorphic, and when present, their rate is often fairly steady at or above 220 beats/min. For children with SVT and good perfusion, vagal maneuvers can be attempted. In cases in which SVT is associated with poor perfusion, providers should rapidly move to convert the child’s heart rhythm back to sinus rhythm. If the child already has IV access, then adenosine can be given via IV with rapid “push.” Adenosine has an extremely short half-life, so a proximal IV is best, and the adenosine should be set up with a 3-way stopcock so it can be given and immediately flushed into the circulation. If the child does not have IV access, adenosine does

<table>
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<th>Table 67-4</th>
<th>Rapid Sequence Intubation</th>
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<tr>
<td><strong>STEP</strong></td>
<td><strong>PROCEDURE</strong></td>
</tr>
<tr>
<td>1</td>
<td>Obtain a brief history and perform an assessment</td>
</tr>
<tr>
<td>2</td>
<td>Assemble equipment, medications, etc.</td>
</tr>
<tr>
<td>3</td>
<td>Preoxygenate the patient</td>
</tr>
<tr>
<td>4</td>
<td>Premedicate the patient with lidocaine, atropine</td>
</tr>
<tr>
<td>5</td>
<td>Induce sedation and analgesia</td>
</tr>
<tr>
<td>6</td>
<td>Pretreat with nondepolarizing paralytic agent</td>
</tr>
<tr>
<td>7</td>
<td>Administer muscle relaxants</td>
</tr>
<tr>
<td>8</td>
<td>Perform a Sellick maneuver</td>
</tr>
<tr>
<td>9</td>
<td>Perform endotracheal intubation</td>
</tr>
<tr>
<td>10</td>
<td>Secure the tube and verify the position with a roentgenogram</td>
</tr>
<tr>
<td>11</td>
<td>Begin mechanical ventilation</td>
</tr>
</tbody>
</table>

ET, endotracheal tube; ICP, intracranial pressure.
not successfully convert the heart rhythm back to sinus rhythm, then synchronized cardioversion, using 0.5-1.0 joule/kg, should be performed. In cases of wide complex tachycardia, providers should move immediately to cardioversion and increase the dose to 2 joules/kg if 1 joule/kg is not effective. As with cases of bradycardia, providers should review the 6 Hs and 5 Ts to identify factors that might be contributing to the tachycardia (see Table 67-5).

RECOGNITION AND MANAGEMENT OF CARDIAC ARREST

Cardiac arrest occurs when the heart fails as an effective pump and blood flow ceases. Outwardly, the patient in cardiac arrest presents as unresponsive and apneic with no palpable pulse. Internally, the cessation of nutrient flow causes progressive tissue ischemia and organ dysfunction. If not rapidly reversed, cardiac arrest leads to progressive deterioration in brain and heart function such that resuscitation and recovery are no longer possible.

Pediatric cardiac arrest is rarely caused by a sudden coronary event or arrhythmia. Instead, cardiac arrest in children is most often the end result of progressive asphyxia, caused by tissue hypoxia, acidosis, and nutrient depletion at the end stages of respiratory deterioration, shock, or heart failure. Therefore, the most important treatment of cardiac arrest is anticipation and preventive: Intervening when a child manifests respiratory distress or early stages of shock can prevent deterioration to full-blown arrest. When sudden cardiac arrest does occur, it is most often associated with an arrhythmia, specifically ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT). In sudden events such as these, the key to successful resuscitation is early
<table>
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<tr>
<th>CONDITION</th>
<th>COMMON CLINICAL SETTINGS</th>
<th>CORRECTIVE ACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acidosis</td>
<td>Preexisting acidosis, diabetes, diarrhea, drugs and toxins, prolonged resuscitation, renal disease, and shock</td>
<td>Reassess the adequacy of cardiopulmonary resuscitation, oxygenation, and ventilation; reconfirm endotracheal tube placement. Hyperventilate. Consider intravenous bicarbonate if pH &lt; 7.2 after above actions have been taken.</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>Hemorrhagic diathesis, cancer, pericarditis, trauma, after cardiac surgery, and after myocardial infarction</td>
<td>Administer fluids; obtain bedside echocardiogram, if available. Perform pericardiocentesis; immediate surgical intervention is appropriate if pericardiocentesis is unhelpful but cardiac tamponade is known or highly suspected.</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>Alcohol abuse, burns, central nervous system disease, debilitated patient, drowning, drugs and toxins, endocrine disease, history of exposure, homelessness, extensive skin disease, spinal cord disease, and trauma</td>
<td>If hypothermia is severe (temperature &lt; 30°C [86°F]), limit initial shocks for ventricular fibrillation or pulseless ventricular tachycardia to 3; initiate active internal rewarming and cardiopulmonary support. If hypothermia is moderate (temperature 30-34°C [86-93.2°F]), proceed with resuscitation (space medications at longer intervals than usual), passively rewarm child, and actively warm truncal body areas.</td>
</tr>
<tr>
<td>Hypovolemia, hemorrhage, anemia</td>
<td>Major burns, diabetes, gastrointestinal losses, hemorrhage, hemorrhagic diathesis, cancer, pregnancy, shock, and trauma</td>
<td>Administer fluids. Transfuse packed red blood cells if hemorrhage or profound anemia is present. Thoracotomy is appropriate when a patient has cardiac arrest from penetrating trauma and a cardiac rhythm and the duration of cardiopulmonary resuscitation before thoracotomy is &lt; 10 min.</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>Consider in all patients with cardiac arrest</td>
<td>Reassess the technical quality of cardiopulmonary resuscitation, oxygenation, and ventilation; reconfirm endotracheal tube placement.</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>Alcohol abuse, burns, diabetic ketoacidosis, severe diarrhea, diuretics, and drugs (e.g., cisplatin, cyclosporine, pentamidine)</td>
<td>Administer 1-2 g magnesium sulfate IV over 2 min.</td>
</tr>
<tr>
<td>Poisoning</td>
<td>Alcohol abuse, bizarre or puzzling behavioral or metabolic presentation, classic toxicologic syndrome, occupational or industrial exposure, and psychiatric disease</td>
<td>Consult a toxicologist for emergency advice on resuscitation and definitive care, including an appropriate antidote. Prolonged resuscitation efforts may be appropriate; immediate cardiopulmonary bypass should be considered, if available.</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Metabolic acidosis, excessive administration of potassium, drugs and toxins, vigorous exercise, hemolysis, renal disease, rhabdomyolysis, tumor lysis syndrome, and clinically significant tissue injury</td>
<td>If hyperkalemia is identified or strongly suspected, treat* with all of the following: 10% calcium chloride (5-10 mL by slow IV push; do not use if hyperkalemia is secondary to digitalis poisoning), glucose and insulin (50 mL of 50% dextrose in water and 10 units of regular insulin IV), sodium bicarbonate (50 mmol IV; most effective if concomitant metabolic acidosis is present), and albuterol (15-20 mg nebulized or 0.5 mg by IV infusion).</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>Alcohol abuse, diabetes, use of diuretics, drugs and toxins, profound gastrointestinal losses, hypomagnesemia</td>
<td>If profound hypokalemia (&lt; 2.0-2.5 mmol of potassium) is accompanied by cardiac arrest, initiate urgent IV replacement (2 mmol/min IV for 10-15 mmol)*; then reassess.</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>Hospitalized patient, recent surgical procedure, peripartum, known risk factors for venous thromboembolism, history of venous thromboembolism, or prearrest presentation consistent with a diagnosis of acute pulmonary embolism</td>
<td>Administer fluids; augment with vasopressors as necessary. Confirm the diagnosis, if possible; consider immediate cardiopulmonary bypass to maintain patient’s viability. Consider definitive care (e.g., thrombolytic therapy, embolectomy by interventional radiology or surgery).</td>
</tr>
<tr>
<td>Tension pneumothorax</td>
<td>Placement of a central catheter, mechanical ventilation, pulmonary disease (including asthma, chronic obstructive pulmonary disease, and necrotizing pneumonia), thoracentesis, and trauma</td>
<td>Needle decompression, followed by chest tube insertion.</td>
</tr>
</tbody>
</table>

*Adult dose. Adjust for size of child. See Table 67-6.

Cardiac arrest is recognized from general and primary survey findings consistent with a pale or cyanotic child who is unresponsive, apneic, and pulseless. Even experienced providers have a relatively high error rate when asked to determine presence or absence of pulse in a child. Therefore, any child found unresponsive and apneic can be presumed to be in cardiac arrest, and a rescuer should respond accordingly.

A lone rescuer for an unwitnessed pediatric cardiac arrest in an outpatient setting should treat the arrest as asphyxial in nature and should immediately initiate CPR. The rescuer should perform recognition of the arrhythmia and prompt treatment with high-quality CPR and defibrillation.

The principle behind high-quality CPR is that adequate chest compressions—those that circulate blood around the body with a good pulse pressure—are the most important component of CPR. The caregiver providing chest compressions should push hard, push fast, allow for complete chest recoil, and minimize interruptions. Ideally, chest compressions should be interrupted only for ventilation, a rhythm check, or delivery of a defibrillating shock.
initial rescue breaths and 2 min of chest compressions and ventilations before leaving the child to activate the emergency response system. For an in-hospital arrest, the provider should call for help and send someone else to activate the emergency response system while beginning CPR. A lone rescuer in an outpatient setting who witnesses a child’s sudden collapse should treat the arrest as a primary arrhythmia, should immediately activate the EMS system, and should obtain an AED. Upon returning to the child, the rescuer should confirm pulselessness, turn on the AED, place the leads on the child’s chest, and follow the defibrillator’s voice commands.

The initial step in CPR for a child of any age is to restore ventilation and oxygenation as quickly as possible. Upon confirmation of unresponsiveness, apnea, and pulselessness, the provider should open the airway with a head-tilt/chin-lift maneuver (or jaw-thrust if cervical spine trauma is suspected) and provide 2 initial rescue breaths (Fig. 67-14). These breaths are deep and slow, lasting approximately 1 sec per breath. The breaths are adequate if they cause the chest to rise and fall and improve the child’s color. If the breaths appear inadequate, the child should be repositioned, and the breaths delivered again. If the breaths remain ineffective, the provider should assess the child for foreign body aspiration. After 2 effective rescue breaths, the child’s pulse should be assessed. If the child has a pulse but remains apneic (or with ineffective breathing), then the rescuer should continue to provide assisted ventilation at an age-appropriate rate. Infants and children ≤ 1 y r old should receive rescue breathing at a rate of roughly 15-20 breaths/min, or roughly 1 breath every 3-5 sec. Children > 1 y r old should receive 10-12 breaths/min, or 1 breath every 5-6 sec.

If the child remains pulseless, chest compressions should be initiated. Chest compressions in infants < 1 yr old may be performed by placing 2 thumbs on the midsternum with the hands encircling the thorax or by placing 2 fingers over the midsternum and compressing (Figs. 67-15 and 67-16). For children > 1 yr old, the care provider should perform chest compressions over the lower half of the sternum with the heel of 1 hand, or with 2 hands as used for adult resuscitation (Fig. 67-17). In all cases, care should be taken to avoid compression of the xiphoid and the ribs. When feasible, a cardiac resuscitation board (Fig. 67-18). In all cases, care should be taken to avoid compression of the xiphoid and the ribs. When feasible, a cardiac resuscitation board

Figure 67-14 Combined jaw-thrust/spine stabilization maneuver for the pediatric trauma victim. (From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part V. Pediatric basic life support, JAMA 268:2251–2261, 1992.)

at a level that is compatible with survival. If resuscitative efforts do not succeed in reestablishing life-sustaining breathing and circulation, the medical team must decide whether continued efforts are warranted or whether the resuscitation should be stopped. If EMS care is en route, bringing the potential for further escalation in care such as endotracheal intubation, vascular access, and medications, CPR should be continued as long as possible or deemed reasonable by the rescuers.

In the in-hospital setting, the ECG should dictate further resuscitative efforts. For children without a pulse and in asystole or electromechanical dissociation (pulseless electrical activity), providers should continue rescue breathing and CPR, obtain vascular access, and give emergency IV epinephrine (Fig. 67-18). For continued asystole or pulseless electrical activity, epinephrine can be repeated every 3-5 min. Patient history, physical exam findings, and laboratory evaluation should be used to elicit correctable causes of arrest (such as the 6 Hs and 5 Ts) (see Table 67-5). CPR should be continued after epinephrine administration, to circulate the drug through the body. After 5 cycles of CPR, providers should reassess the child for the presence of a pulse or a change in the ECG rhythm that would necessitate a different response.

For those children with pulseless VT or VF, emergency defibrillation is indicated (see Fig. 67-18). Providers should apply the pads to the child’s bare chest and back and follow the verbal instructions given by the AED. For younger children, a defibrillator (if available) set to the dose of 2 joules/kg should be used. Ideally, the AED used in a child
Traditionally, continuing CPR >20 min in children with in-hospital cardiac arrest has been considered futile. With current practice for CPR, survival for in-hospital cardiac arrest is approximately 40% for CPR duration <15 min compared with approximately 12% for CPR lasting >35 min. Survivors had a favorable neurologic outcome in 70% with a CPR duration <15 min compared with 60% for those requiring resuscitation for >35 min.

VASCULAR ACCESS

Venous Access
Veins suitable for cannulation are numerous, but there is considerable anatomic variation from patient to patient. In the upper extremities, the median antecubital vein, located in the antecubital fossa, is often the largest and easiest to access (Fig. 67-19). Many veins on the dorsum of the hand are also suitable for cannulation because they are often large and easily located on the flat surface of the dorsum of the hand, and their cannulation is well tolerated. The cephalic vein is usually cannulated at the wrist, along the forearm, or at the elbow. The median vein of the forearm is also suitable because it lies along a flat surface of the forearm. In the lower extremity, the great saphenous vein, located just anterior to the medial malleolus, is accessible in most patients. The dorsum of the foot usually has a large vein in the midline, passing across the ankle joint, but catheters are difficult to maintain in this vein because dorsiflexion tends to dislodge them. A second large vein on the lateral side of the foot, running in the horizontal plane, usually 1-2 cm dorsal to the lower margin of the foot, is preferable (Fig. 67-20). The most notable scalp veins are the superficial temporal (just anterior to the ear) and posterior auricular (just behind the ear).

Deeper and larger central veins can provide more reliable, large-bore access for medications, nutritive solutions, and blood sampling than peripheral venous lines. They may be reached by percutaneous cannulation or surgical exposure. In infants and young children, the femoral vein is often the easiest to access and cannulate, but the internal jugular and subclavian veins may also be used (Figs. 67-21 and 67-22). Because of its proximity to the median nerve, the brachial vein is not often recommended for cannulation.

Intraosseous Access
Intraosseous (IO) needles (for intramedullary venous plexus access) are special rigid, large-bore needles that resemble those used for bone marrow aspiration. IO cannulation is recommended for patients for whom IV access proves difficult or unattainable, even in older children. If venous access is not available within 1 min in a child with cardio-pulmonary arrest, an IO needle should be placed in the anterior proximal tibia (with care taken to avoid traversing the epiphyseal plate). The needle should penetrate the anterior layer of compact bone, and its tip

≤8 yr of age should be equipped with an attenuated adult dose or should be designed for children; if neither device is available, a standard adult AED should be used. CPR should be immediately restarted after defibrillation. Emergency dose epinephrine can also be administered with another 5 cycles of CPR to ensure its circulation throughout the child’s body. If the ECG rhythm continues to show VF or VT, defibrillation can be alternated with epinephrine. For refractory VF or VT, an IV antiarrhythmic, such as amiodarone or lidocaine, can be given (Tables 67-6 and 67-7).

New approaches to CPR in adults have highlighted the potential value of bystander chest compression alone in the initial resuscitation in a community setting. In addition, the combination of vasopressin, methylprednisolone, and epinephrine during an in-hospital cardiac arrest followed by hydrocortisone during the postresuscitation shock period has resulted in a better outcome than patients treated with epinephrine alone. Whether these observations are applicable to young children, who often have different etiologies for cardiopulmonary arrest, has not been determined.
Figure 67-18 Pediatric advanced life support pulseless arrest algorithm. (From Kleinman ME, Chameides L, Schexnayder SM, et al: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, part 14, Circulation 122[Suppl 3]: S876–S908, 2010, Fig. 1, p. S885.)
### Table 67-6  Medications for Pediatric Resuscitation and Arrhythmias

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>DOSE</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine</td>
<td>0.1 mg/kg (maximum 6 mg)</td>
<td>Monitor ECG; Rapid IV/IO bolus</td>
</tr>
<tr>
<td></td>
<td>Repeat: 0.2 mg/kg (maximum 12 mg)</td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>5 mg/kg IV/IO; repeat up to 15 mg/kg</td>
<td>Monitor ECG and blood pressure; Adjust administration rate to urgency;</td>
</tr>
<tr>
<td></td>
<td>Maximum: 300 mg</td>
<td>give more slowly when perfusing rhythm is present; Use caution when</td>
</tr>
<tr>
<td></td>
<td></td>
<td>administering with other drugs that prolong QT interval; consider</td>
</tr>
<tr>
<td></td>
<td></td>
<td>expert consultation</td>
</tr>
<tr>
<td>Atropine</td>
<td>0.02 mg/kg IV/IO</td>
<td>Higher doses may be used with organophosphate poisoning</td>
</tr>
<tr>
<td></td>
<td>0.03 mg/kg ET*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Repeat once if needed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minimum dose: 0.1 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minimum single dose:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Child, 0.5 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adolescent, 1 mg</td>
<td></td>
</tr>
<tr>
<td>Calcium chloride (10%)</td>
<td>20 mg/kg IV/IO (0.2 mL/kg)</td>
<td>Slowly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adult dose: 5-10 mL</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.01 mg/kg (0.1 mL/kg 1:10,000) IV/IO</td>
<td>May repeat q 3-5 min</td>
</tr>
<tr>
<td></td>
<td>0.1 mg/kg (0.1 mL/kg 1:1,000) ET*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximum dose: 1 mg IV/IO; 10 mg ET</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>0.5-1 g/kg IV/IO</td>
<td>D10W: 5-10 mL/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D25W: 2-4 mL/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D50W: 1-2 mL/kg</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Bolus: 1 mg/kg IV/IO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximum dose: 100 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infusion: 20-50 µg/kg/min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ET*: 2-3 mg</td>
<td></td>
</tr>
<tr>
<td>Magnesium sulfate</td>
<td>25-50 mg/kg IV/IO over 10-20 min; faster in</td>
<td></td>
</tr>
<tr>
<td></td>
<td>torsades de pointes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximum dose: 2g</td>
<td></td>
</tr>
<tr>
<td>Naloxone</td>
<td>&lt;5 yr or ≤20 kg: 0.1 mg IV/IO/ET*</td>
<td>Use lower doses to reverse respiratory depression associated with</td>
</tr>
<tr>
<td></td>
<td>≥5 yr or &gt;20 kg: 2 mg IV/IO/ET*</td>
<td>therapeutic opioid use (1-15 µg/kg)</td>
</tr>
<tr>
<td>Procainamide</td>
<td>15 mg/kg IV/IO over 30-60 min</td>
<td>Monitor ECG and blood pressure; Use caution when administering with</td>
</tr>
<tr>
<td></td>
<td>Adult dose: 20 mg/min IV infusion up to total</td>
<td>other drugs that prolong QT interval; consider expert consultation</td>
</tr>
<tr>
<td></td>
<td>maximum dose of 17 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>1 mEq/kg/dose IV/IO slowly</td>
<td>After adequate ventilation</td>
</tr>
</tbody>
</table>

*Flush with 5 mL of normal saline and follow with 5 ventilations.
ECG, electrocardiogram; ET, endotracheal tube; IO, intraosseous; IV, intravenous.


### Table 67-7  Medications to Maintain Cardiac Output and for Postresuscitation Stabilization

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>DOSE RANGE</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inamrinone</td>
<td>0.75-1 mg/kg IV/IO over 5 min; may repeat 2x;</td>
<td>Inodilator</td>
</tr>
<tr>
<td></td>
<td>then: 2-20 µg/kg/min</td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td>2-20 µg/kg/min IV/IO</td>
<td>Inotrope; vasodilator</td>
</tr>
<tr>
<td>Dopamine</td>
<td>2-20 µg/kg/min IV/IO in low doses; pressor in</td>
<td>Inotrope; chronotrope; renal and splanchnic vasodilator</td>
</tr>
<tr>
<td></td>
<td>higher doses</td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.1-1 µg/kg/min IV/IO</td>
<td>Inotrope; chronotrope; vasodilator; vasopressor in higher doses</td>
</tr>
<tr>
<td>Milrinone</td>
<td>50-75 µg/kg IV/IO over 10-60 min then 0.5-0.75</td>
<td>Inodilator</td>
</tr>
<tr>
<td></td>
<td>µg/kg/min</td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0.1-2 µg/kg/min</td>
<td>Inotrope; vasopressor</td>
</tr>
<tr>
<td>Sodium nitroprusside</td>
<td>1-8 µg/kg/min</td>
<td>Vasodilator; prepare only in DSW</td>
</tr>
</tbody>
</table>

*Alternative formula for calculating an infusion: Infusion rate (mL/hr) = [weight (kg) x dose (µg/kg/min) x 60 (min/hr)]/concentration (µg/mL).
D5W, 5% dextrose in water; IO, intraosseous; IV, intravenous.

advanced into the spongy interior of the bone (Fig. 67-23). Commercially available IO kits frequently include drills that obviate the complications of needle placement associated with manual placement. Any and all medications, blood products, and fluids may be administered through the IO route, including all medications required for emergency resuscitation. Complications are uncommon, but may include osteomyelitis with prolonged infusions and tibial fracture.

### Arterial Access

Arterial access is indicated when care providers need frequent blood sampling, particularly to assess adequacy of oxygenation, ventilation, or acid–base balance, and/or continuous blood pressure monitoring. The radial artery, the most commonly cannulated artery, lies on the lateral side of the anterior wrist, just medial to the styloid process of the radius (Fig. 67-24). The ulnar artery, just lateral to the tendon of the flexor carpi ulnaris, is used less often because of its proximity to the ulnar nerve. Useful sites in the lower extremity, particularly in neonates and infants, are the dorsalis pedis artery, on the dorsum of the foot between the tendons of the tibialis anterior and the extensor hallucis longus, and the posterior tibial artery, posterior to the medial...
Thoracentesis and Chest Tube Placement

Thoracentesis is the placement of a needle or catheter into the pleural space to evacuate fluid, blood, or air. Most insertions are performed in one of the intercostal spaces between the 4th and 9th ribs in the plane of the midaxillary line. After appropriate systemic and local anesthesia/sedation is performed as clinically indicated, a skin incision is made, and dissection through the chest wall is accomplished in layers with use of blunt dissection techniques. The needle (and later, the chest tube) that enters the pleural space should penetrate the intercostal space by passing over the superior edge of the lower rib, because there are larger vessels along the inferior edge of the rib. Ideally, the chest tube should lie anterior in the pleural space for air accumulation, and posterior for fluid accumulation. A radiograph must be obtained to verify chest tube placement and evacuation of the pleural space.

Pericardiocentesis

When fluid, blood, or gas accumulates in the pericardial sac, a danger is that the heart will be compressed and will not be able to fill and empty with normal volumes of blood, leading to diminished cardiac output. The cardinal signs of such a restrictive pericardial effusion are tachycardia, hypotension, and decreasing oxygen saturation. Pericardiocentesis includes needle aspiration of the pericardial sac, often followed by the placement of a catheter for continuous drainage. As for thoracentesis, chest radiography should be done to confirm catheter location as well as to evaluate for presence of any complications, such as pneumothorax or hemothorax.

POSTRESUSCITATION CARE

After successful resuscitation, close observation in an intensive care unit, where the child can receive ongoing mult орган system assessments and support, is critical. Optimal postresuscitation care includes ongoing support of cardiovascular and respiratory system function as needed and the identification and treatment of other organ system dysfunction that may have contributed to (or resulted from) the child’s cardiopulmonary instability. Good postresuscitation intensive care also includes supportive services for the child’s parents, siblings, family, and friends.

Induced hypothermia (32-34°C [89.6-91.4°F] for \( \approx 48 \) hr) may improve survival and neurologic function in adult and pediatric survivors of CPR. This is a controversial treatment that has inconsistently proven beneficial in comatose adult survivors of cardiac arrest. Randomized clinical trials in children are in progress. Furthermore, hypothermia must be avoided. Hypoxic-ischemic encephalopathy with subsequent development of seizures, intellectual impairment, and spasticity, is a serious and common complication of cardiac arrest. In addition hyperglycemia and hypoglycemia should be avoided.

Postresuscitation management generally has 2 phases, similar to earlier, emergency resuscitative care. First, the providers must assess the child’s airway and breathing and must support oxygenation and ventilation as indicated. If the child has ongoing respiratory failure and has been supported with bag-valve-mask ventilation until this time, the providers should now move forward with intubation. Once the child is intubated, mechanical ventilation must be established, and respiratory assessments performed, such as chest radiography and arterial blood gas sampling and analysis. The child’s circulatory system must also be assessed and supported as needed. Continuous arterial blood pressure monitoring can help the provider determine the need for, and response to, inotropic and chronotropic medications (see Table 67-7). Once the ABCs have been managed, providers can move on to full organ system assessments. A systematic approach that employs a full physical exam and laboratory evaluation to reveal the child’s respiratory, cardiovascular, neurologic, gastrointestinal, renal, and hematologic system function should be used.

Communication with the family is an essential element of postresuscitation care. The family should be thoroughly briefed on the elements of the resuscitation performed, the child’s condition, and ongoing medical concerns, uncertainties, or issues by the most senior provider available. This provider should be available to answer the family’s questions, clarify information, and provide comfort. Other support staff, such as social workers and chaplains, should be contacted, as the family wishes, to provide additional support and comfort. For situations in which the resuscitation is ongoing and the child is not expected to survive, the American Academy of Pediatrics recommends that the provider make every effort possible to have the family present at the bedside if they wish. Family presence during CPR or other emergency resuscitative efforts, even if the child dies, is associated with a more positive medical experience than if they are excluded. In cases in which the child is critically ill but stable, the family should be brought to the bedside as soon as the healthcare team deems it safe and appropriate.

Bibliography is available at Expert Consult.
Bibliography


NEUROCRITICAL CARE PRINCIPLES

The brain has high metabolic demands, which are further increased during growth and development. Preservation of nutrient supply to the brain is the mainstay of care for children with evolving brain injuries. Intracranial dynamics describes the physics of the interactions of the contents—brain parenchyma, blood (arterial, venous, capillary) and cerebrospinal fluid (CSF)—within the cranium. Normally, brain parenchyma accounts for up to 85% of the contents of the cranial vault, and the remaining portion is divided between CSF and blood. The brain resides in a relatively rigid cranial vault, and cranial compliance decreases with age as the skull ossification centers gradually replace cartilage with bone. The intracranial pressure (ICP) is derived from the volume of its components and the bony compliance. The perfusion pressure of the brain (cerebral perfusion pressure [CPP]) is equal to the pressure of blood entering the cranium (mean arterial pressure) minus the ICP, in most cases.

Increases in intracranial volume can result from swelling, masses, or increases in blood and CSF volumes. As these volumes increase, compensatory mechanisms decrease ICP by (a) decreasing CSF volume (CSF is displaced into the spinal canal or absorbed by arachnoid villi), (b) decreasing cerebral blood volume (venous blood return to the thorax is augmented), and/or (c) increasing cranial volume (sutures pathologically expand or bone is remodeled). Once compensatory mechanisms are exhausted (the increase in cranial volume is too large), small increases in volume lead to large increases in ICP or intracranial hypertension (Fig. 68-1). As ICP continues to increase, brain ischemia can occur as CPP falls. Further increases in ICP can ultimately displace the brain downward into the foramen magnum—a process called cerebral herniation, which can become irreversible in minutes and may lead to severe disability or death; Figure 68-2 notes other sites of brain herniation.

Oxygen and glucose are required by brain cells for normal functioning, and these nutrients must be constantly supplied by cerebral blood flow (CBF). Normally, CBF is constant over a wide range of blood pressures (blood pressure autoregulation of CBF) via actions mainly within the cerebral arterioles. Cerebral arterioles are maximally dilated at lower blood pressures and maximally constricted at higher pressures so that CBF does not vary during normal fluctuations (Fig. 68-3). Acid–base balance of the CSF (often reflected by acute changes in arterial partial pressure of carbon dioxide [PaCO₂]), body/brain temperature, glucose utilization, and other vasoactive mediators (i.e., adenosine, nitric oxide) can also affect the cerebral vasculature.

Figure 68-1 The Munro-Kellie doctrine describes intracranial dynamics in the setting of an expanding mass lesion (i.e., hemorrhage, tumor) or brain edema. In the normal state, the brain parenchyma, arterial blood, CSF, and venous blood occupy the cranial vault at a low pressure, generally <10 mm Hg. With an expanding mass lesion or brain edema, initially there is a compensated state as a result of reduced CSF and venous blood volumes, and ICP remains low. Further expansion of the lesion, however, leads to an uncompensated state when compensatory mechanisms are exhausted and intracranial hypertension results. See text for details.

Figure 68-2 Different forms of brain herniation. 1, Cingulate. 2, Uncal. 3, Cerebellar tonsillar. 4, Upward cerebellar. 5, Transcalvarial. (From Fishman RA: Cerebrospinal fluid in diseases of the nervous system, Philadelphia, 1980, Saunders.)

Figure 68-3 Schematic of the relationship between CBF and CPP. The diameter of a representative cerebral arteriole is also shown across the center of the y axis to facilitate understanding of the vascular response across CPP that underlies blood pressure autoregulation of CBF. CPP is generally defined as the mean arterial pressure (MAP) minus the ICP. At normal values for ICP, this generally represents MAP. Thus, normally, CBF is kept constant between the lower limit and upper limit of autoregulation; in normal adults, these values are ≈50 mm Hg and 150 mm Hg, respectively. In children, the upper limit of autoregulation is likely proportionally lower than the adult value relative to normal MAP for age. However, according to the work of Vavilala et al. (2003), lower limit values are surprisingly similar in infants and older children. Thus, infants and young children may have less reserve for adequate CPP. See text for details.
Knowledge of these concepts is instrumental to preventing secondary brain injury. Increases in CSF pH that occur because of inadvertent hyperventilation (decreased Paco₂) can produce cerebral ischemia. Hyperthermia-mediated increases in cerebral metabolic demands may damage vulnerable brain regions after injury. Hypoglycemia can produce neuronal death when CBF fails to compensate. Prolonged seizures can lead to permanent injuries if hypoxemia occurs from loss of airway control.

Attention to detail and constant reassessment are paramount in managing children with critical neurologic insults. Among the most valuable tools for serial, objective assessments of neurologic condition is the Glasgow Coma Scale (GCS) (see Table 67-3 in Chapter 67). Originally developed to assess level of consciousness after traumatic brain injury (TBI) in adults, the GCS is also valuable in pediatrics. Modifications to the GCS have been made for nonverbal children and are available for infants and toddlers (see Table 67-3 in Chapter 67). Serial assessments of the GCS score along with a focused neurologic examination are invaluable to detection of injuries before permanent damage occurs in the vulnerable brain.

The FOUR (full outline of unresponsiveness) score (Table 68-1) is a modification of the GCS, which eliminates the verbal response but adds two functional assessments of the brain stem (pupil, corneal, cough reflexes, and respiratory patterns).

The most-studied monitoring device in clinical practice is the ICP monitor. Monitoring is accomplished by a catheter inserted either into the cerebral ventricle (externalized ventricular drain) or into brain parenchyma (parenchymal transducer). ICP-directed therapies are standard of care in TBI and are used in other conditions, such as intracranial hemorrhage. Rye syndrome, and some cases of encephalopathy, meningitis, and encephalitis. Other devices being used include catheters that measure brain tissue oxygen concentration, external probes that noninvasively assess brain oxygenation by absorbance of near-infrared light (near-infrared spectroscopy), monitors of brain electrical activity (continuous electroencephalography [EEG] or somatosensory, visual, or auditory evoked potentials), and CBF monitors (transcranial Doppler, xenon CT, perfusion MRI, or tissue probes).

In the current severe TBI guidelines, brain tissue oxygen concentration monitoring received level III support and thus, may be considered.

### Traumatic Brain Injury

#### Etiology

Mechanisms of TBI include motor vehicle crashes, falls, assaults, and abusive head trauma. Most TBIs in children are from closed-head injuries.

#### Epidemiology

TBI is an important pediatric public health problem, with approximately 37,000 cases resulting in the death of more than 7,000 children annually in the United States.

#### Pathology

Epidural, subdural, and parenchymal intracranial hemorrhages can result. Injury to gray or white matter is also commonly seen and includes focal cerebral contusions, diffuse cerebral swelling, axonal injury, and injury to the cerebellum or brainstem. Patients with severe TBI often have multiple findings; diffuse and potentially delayed cerebral swelling is common.

#### Pathogenesis

TBI results in primary and secondary injury. Primary injury from the impact produces irreversible tissue disruption. In contrast, 2 types of secondary injury are targets of neurointensive care. First, some of the ultimate damage seen in the injured brain evolves over hours or days, and the underlying mechanisms involved (edema, apoptosis, and secondary axotomy) are therapeutic targets. Second, the injured brain is vulnerable to additional insults because injury disrupts normal autoregulatory defense mechanisms; disruption of autoregulation of CBF can lead to ischemia from hypotension that would otherwise be tolerated by the uninjured brain.

<table>
<thead>
<tr>
<th>Table 68-1</th>
<th>Commonly Used Coma Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GLASGOW COMA SCALE</strong></td>
<td><strong>FULL OUTLINE OF UNRESPONSIVENESS (FOUR) SCORE</strong></td>
</tr>
<tr>
<td><strong>Eye Opening</strong></td>
<td><strong>Eye Response</strong></td>
</tr>
<tr>
<td>1 = does not open eyes</td>
<td>4 = eyelids open or opened, tracking, or blinking to command</td>
</tr>
<tr>
<td>2 = opens eyes in response to noxious stimuli</td>
<td>3 = eyelids open but not tracking</td>
</tr>
<tr>
<td>3 = opens eyes in response to voice</td>
<td>2 = eyelids closed but open to loud voice</td>
</tr>
<tr>
<td>4 = opens eyes spontaneously</td>
<td>1 = eyelids closed but open to pain</td>
</tr>
<tr>
<td><strong>Verbal Output</strong></td>
<td>0 = eyelids remain closed with pain</td>
</tr>
<tr>
<td>1 = makes no sounds</td>
<td><strong>Motor Response</strong></td>
</tr>
<tr>
<td>2 = makes incomprehensible sounds</td>
<td>4 = thumbs-up, fist, or peace sign</td>
</tr>
<tr>
<td>3 = utters inappropriate words</td>
<td>3 = localizing to pain</td>
</tr>
<tr>
<td>4 = confused and disoriented</td>
<td>2 = flexion response to pain</td>
</tr>
<tr>
<td>5 = speaks normally and oriented</td>
<td>1 = extension response to pain</td>
</tr>
<tr>
<td><strong>Motor Response (Best)</strong></td>
<td>0 = no response to pain or generalized myoclonus status</td>
</tr>
<tr>
<td>1 = makes no movements</td>
<td><strong>Brainstem Reflexes</strong></td>
</tr>
<tr>
<td>2 = extension to painful stimuli</td>
<td>4 = pupil and corneal reflexes present</td>
</tr>
<tr>
<td>3 = abnormal flexion to painful stimuli</td>
<td>3 = one pupil wide and fixed</td>
</tr>
<tr>
<td>4 = flexion/withdrawal to painful stimuli</td>
<td>2 = pupil or corneal reflexes absent</td>
</tr>
<tr>
<td>5 = localized to painful stimuli</td>
<td>1 = pupil and corneal reflexes absent</td>
</tr>
<tr>
<td>6 = obey commands</td>
<td>0 = absent pupil, corneal, and cough reflex</td>
</tr>
<tr>
<td><strong>Respiration</strong></td>
<td><strong>Apnea</strong></td>
</tr>
<tr>
<td>4 = not intubated, regular breathing pattern</td>
<td>0 = absent ventilator rate or apnea</td>
</tr>
<tr>
<td>3 = not intubated, Cheyne-Stokes breathing pattern</td>
<td></td>
</tr>
<tr>
<td>2 = not intubated, irregular breathing</td>
<td></td>
</tr>
<tr>
<td>1 = breathes above ventilatory rate</td>
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</table>


### Clinical Manifestations

The hallmark of severe TBI is coma (GCS score 3-8). Often, coma is seen immediately after the injury and is sustained. In some cases, such as with an epidural hematoma, a child may be alert on presentation but may deteriorate after a period of hours. A similar picture can be seen in children with diffuse swelling, in whom a talk-and-die scenario has been described. Clinicians should also not be lulled into underappreciating the potential for deterioration of a child with moderate TBI (GCS score 9-12) with a significant contusion, because progressive swelling can potentially lead to devastating complications. In the comatose child with severe TBI, the second key clinical manifestation is the development of intracranial hypertension. The development of increased ICP with impending herniation may be heralded by new-onset or worsening headache, depressed level of consciousness, vital sign changes (hypertension, bradycardia, irregular respirations), and signs of 6th (lateral rectus palsy) or 3rd (anisocoria [dilated pupil], ptosis, down-and-out position of globe as a result of rectus muscle palsies) cranial nerve compression. Increased ICP is managed with continuous ICP monitoring, as well as monitoring for clinical signs of increased ICP or impending herniation. The development of brain swelling is progressive. Significantly raised ICP (>20 mm Hg) can occur early after severe TBI, but peak ICP generally is seen at 48-72 hr.
Diagnosis and Differential Diagnosis

In severe TBI, the diagnosis is generally obvious from the history and clinical presentation. Occasionally, TBI severity can be overestimated because of concurrent alcohol or drug intoxication. The diagnosis of TBI can be problematic in cases of abusive head trauma or following an anoxic event such as drowning or smoke inhalation.

Treatment

Infants and children with severe or moderate TBI (GCS score 3-8 or 9-12, respectively) receive intensive care unit (ICU) monitoring. Evidence-based guidelines for management of severe TBI have been published (Fig. 68-12). This approach to ICP-directed therapy is also reasonable for other conditions in which ICP is monitored. Care involves a multidisciplinary team comprising pediatric caregivers from
neurologic surgery, critical care medicine, surgery, and rehabilitation, and is directed at preventing secondary insults and managing raised ICP. Initial stabilization of infants and children with severe TBI includes rapid sequence tracheal intubation with spine precautions along with maintenance of normal extracerebral hemodynamics, including blood gas values (partial pressure arterial oxygen, PaCO₂), mean arterial pressure, and temperature. Intravenous fluid boluses may be required to treat hypotension. Euvolemia is the target, and hypotonic fluids should be rigorously avoided; normal saline is the fluid of choice. Pressors may be needed as guided by monitoring of central venous pressure, with avoidance of both fluid overload and exacerbation of brain edema. A trauma survey should be performed. Once stabilized, the patient should be taken for CT scanning to rule out the need for emergency neurosurgical intervention. If surgery is not

**Figure 68-8** In a 3 mo old child who suffered from abusive head trauma, initial CT imaging (A) demonstrates chronic subdural hematoma bilaterally. Three days after hospitalization (B), the subdural hematomas are slightly larger but infarctions are noted in the posterior areas of brain parenchyma (see arrows).

**Figure 68-9** In a 16 yr old who fell off of his dirt bike, CT imaging demonstrates intraparenchymal hemorrhage and significant surrounding edema (arrow).

**Figure 68-10** An 11 yr old child was hit in the head by a horse, and CT imaging demonstrates multiple, comminuted skull fractures with fragments of bone within the brain parenchyma, multifocal areas of intraparenchymal hemorrhage, and obliteration of the left lateral ventricle.
pentobarbital and either mannitol (0.25-1.0 g/kg IV) or hypertonic saline (3% solution, 5-10 mL/kg IV). ICP should be maintained < 20 mm Hg; age-dependent CPP targets are ≈ 50 mm Hg for children 2-6 yr of age; 55 mm Hg for those 7-10 yr of age; and 65 mm Hg for those 11-16 yr of age. First-tier therapy includes elevation of the head of the bed, ensuring midline positioning of the head, controlled mechanical ventilation, and sedation and analgesia (i.e., benzodiazepines and narcotics). If neuromuscular blockade is needed, it may be desirable to monitor EEG continuously because status epilepticus can occur; this complication will not be recognized if treated promptly.

Figure 68-11 In a 6 yr old child who was hit by a car while riding his bike, initial CT imaging demonstrates no obvious abnormality (A). However, immediate MRI demonstrates multiple areas of punctate hemorrhages (lucencies) consistent with diffuse axonal injury (B, arrows).

Figure 68-12 Schematic outlining the approach to management of a child with severe TBI. It is based on the 2012 guidelines for the management of severe TBI, along with minor modifications from later literature. The ICP and CPP targets are discussed in the text. This schematic is specifically presented for severe TBI, for which the experience with ICP-directed therapy is greatest. Nevertheless, the general approach provided here is relevant to the management of intracranial hypertension in other conditions for which evidence-based data on ICP monitoring and ICP-directed therapy are lacking. Please see text for details.
in a paralyzed patient and is associated with raised ICP and unfavorable outcome. If a ventricular rather than parenchymal catheter is used to monitor ICP, therapeutic CSF drainage is available and can be provided either continuously (often targeting an ICP >5 mm Hg) or intermittently in response to ICP spikes, generally 20 mm Hg. Other first-tier therapies include the osmolar agents mannitol (0.25-1.0 g/kg IV over 20 min), given in response to ICP spikes >20 mm Hg or with a fixed (q4-6h) dosing interval, and hypertonic saline (often given as a continuous infusion of 3% saline at 0.1-1.0 mL/kg/hr). Choice of osmolar agent depends on the preference of the treating center. These 2 agents can be used concurrently. It is recommended to avoid serum osmolality >320 mOsm/L. A Foley urinary catheter should be placed to monitor urine output.

If ICP remains refractory to treatment, careful reassessment of the patient is needed to rule out unrecognized hypercarbia, hypoxemia, fever, hypotension, hypoglycemia, pain, and seizures. Repeat imaging should be considered to rule out a surgical lesion. Guidelines-based second-tier therapies for refractory raised ICP are available, but evidence favoring a given second-tier therapy is limited. In some centers, decompressive craniectomy is used. Others use a pentobarbital infusion, with a loading dose of 5-10 mg/kg over 30 min followed by 5 mg/kg every hour for 3 doses and then maintenance with an infusion of 1 mg/kg/hr. Careful blood pressure monitoring is required because of the possibility of drug-induced hypotension and the frequent need for support with fluids and/or pressors. Mild hypothermia (32–34°C [89.6–93.2°F]) to control refractory ICP can be induced and maintained by means of surface cooling. Sedation and neuromuscular blockade are used to prevent shivering, and rewarming should be slow, no faster than 1°C (1.8°F) every 4-6 hr. Hypotension should be prevented during rewarming. Refractory raised ICP can also be treated with hyperventilation (Paco₂ = 25-30 mm Hg). Other second-tier therapies (e.g., lumbar CSF drainage) are options.

Supportive Care
Euvolemic should be maintained, and isotonic fluids are recommended until resolution of intracranial hypertension. The syndrome of inappropriate antidiuretic hormone secretion and salt wasting can develop and are important to differentiate, because management of the former is fluid restriction and that of the latter is sodium replacement. Severe hyperglycemia (blood glucose level >200 mg/dL) should be avoided and treated. The blood glucose level should be monitored frequently. Early nutrition with enteral feedings is advocated. Corticosteroids should generally not be used unless adrenal insufficiency is documented. Tracheal suctioning can exacerbate raised ICP. Timing of the use of sedation around suctioning events and/or use of tracheal or IV lidocaine can be helpful. Seizures are common after severe acute TBI. Early posttraumatic seizures (within 1 wk) will complicate management of TBI and are often difficult to treat. Anticonvulsant prophylaxis with fosphenytoin, carbamazepine, or levetiracetam is a common treatment option. Late posttraumatic seizures (≥7 days after TBI) and, if recurrent, late posttraumatic epilepsy are not prevented by prophylactic anticonvulsants, whereas early posttraumatic seizures are prevented by initiating anticonvulsants soon after TBI. Antifibrinolytic agents (tranexamic acid) reduce hemorrhage size as well as the development of new focal ischemic cerebral lesions, and improve survival in adults with severe traumatic brain injury.

Prognosis
Mortality rates for children with severe TBI who reach the pediatric ICU range between 10% and 30%. Ability to control ICP is related to patient survival, and the extent of cranial and systemic injuries correlates with quality of life. Motor and cognitive sequelae resulting from severe TBI generally benefit from rehabilitation to minimize long-term disabilities. Recovery from TBI may take months to achieve. Physical therapy, and in some centers methylphenidate, helps with motor and behavioral recovery. Pituitary insufficiency may be an uncommon but significant complication of severe TBI.

Brain death is the irreversible cessation of all functions of the entire brain, including the brainstem. It is also known as the determination of death using neurologic criteria. Although brain death is legally accepted in the United States as the equivalent of death from the irreversible cessation of circulatory and respiratory functions, it can be difficult to understand and is not universally accepted.

Epidemiology
In children, brain death most commonly develops following TBI (including brain injury from nonaccidental trauma) or asphyxial injury. Pathogenesis is multifactorial, with the end result being irreversible loss of brain and brainstem function.

Clinical Manifestations and Diagnosis
Guidelines for the determination of brain death in children were first published in 1987 by a Special Task Force to the American Academy of Pediatrics. These were revised for the first time in 2011 by a combined group from the Society for Critical Care Medicine, the American Academy of Pediatrics, and the Child Neurology Society.

Brain death is primarily a clinical diagnosis. Although ancillary tests such as EEG and CBF studies are sometimes used to assist in making the diagnosis, repeated clinical examination is the standard for diagnosis. The 3 key components of clinical brain death diagnosis are demonstrations of coexisting irreversible coma with a known cause, absence of brainstem reflexes, and apnea.

Before a determination of brain death may be made, it is of utmost importance that the cause of the coma be determined through the use of historical, radiologic, and laboratory data to rule out a reversible condition. Potentially reversible causes of coma include metabolic disorders; toxins; sedative drugs; paralytic agents; hypothermia; hypoxia; hypotension/shock; recent cardiopulmonary resuscitation; hypoglycemia/hyperglycemia; hyponatremia/hypernatremia; hypercalcemia; hypermagnesemia; nonconvulsive status epilepticus; hypothryoidism; hypocortisolism; hypercarbia; liver or renal failure; sepsis; meningitis; encephalitis; subarachnoid hemorrhage; and surgically remediable brainstem lesions. Confounding factors must be corrected prior to initiation of brain death assessment.

Coma
The state of coma requires that the patient be unresponsive, even to noxious stimuli. Any purposeful motor response, such as localization, does not constitute coma. Likewise, any posturing (decerebrate or decorticate) is not consistent with coma, and therefore not consistent with brain death. The presence of spinal cord reflexes—even complex reflexes—does not preclude the diagnosis of brain death.

Brainstem Reflexes
Brainstem reflexes must be absent. Table 68-2 lists the brainstem reflexes to be tested, the brainstem location of each reflex, and the result of each test that is consistent with a diagnosis of brain death.

Apnea
Apnea is the absence of respiratory effort in response to an adequate stimulus. A partial pressure of carbon dioxide (pCO₂) value >260 mm Hg and >20 mm Hg above baseline is considered sufficient. Apnea is clinically confirmed through the apnea test. Because the apnea test has the potential to destabilize the patient, this test is performed only if the first 2 criteria for brain death (irreversible coma and absence of brainstem reflexes) are already confirmed.

The apnea test assesses the function of the medulla in driving ventilation. It is performed by first ensuring appropriate hemodynamics and temperature and the absence of apnea-producing drug effects or significant metabolic derangements. The patient is then preoxygenated with 100% oxygen for approximately 10 minutes and ventilation is adjusted to achieve a pCO₂ of approximately 40 mm Hg. A baseline

Bibliography is available at Expert Consult.
Bibliography

Brainstem Reflex Testing to Determine Brain Death

<table>
<thead>
<tr>
<th>BRAINSTEM REFLEX</th>
<th>AREA TESTED</th>
<th>HOW TO PERFORM THE EXAM</th>
<th>EXPLANATION OF RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pupillary light reflex</td>
<td>CN II and III, midbrain</td>
<td>Shine a light into the eyes while closely observing pupillary size</td>
<td>Midposition (4-6 mm) or fully dilated pupils that are not reactive to light are consistent with brain death. Pinpoint pupils, even if nonreactive, suggest intact function of the Edinger-Westphal nucleus in the midbrain and are therefore not consistent with brain death.</td>
</tr>
<tr>
<td>Oculocephalic reflex (doll’s-eyes reflex)</td>
<td>CN III, VI, and VIII, midbrain, pons</td>
<td>Manually rotate the patient’s head side to side and closely watch the position of the eyes. Should not be performed in a patient with a cervical spine injury.</td>
<td>In an intact patient, the eyes remain fixed on a distant spot, as if maintaining eye contact with that spot. In an exam consistent with brain death, the eyes move in concert with the patient’s head movement.</td>
</tr>
<tr>
<td>Corneal reflex</td>
<td>CN III, V, and VII, pons</td>
<td>Touch the patient’s cornea with a cotton swab.</td>
<td>In the intact patient, the touch results in eyelid closure, and the eye may rotate upward. In an exam consistent with brain death, there is no response.</td>
</tr>
<tr>
<td>Oculovestibular reflex</td>
<td>CN III, IV, VI, and VIII, pons, midbrain</td>
<td>Irrigate the tympanic membrane with iced water or saline and look for eye movement.</td>
<td>Absence of eye movement is consistent with brain death.</td>
</tr>
<tr>
<td>Gag and cough reflex</td>
<td>CN IX and X, medulla</td>
<td>Touch the posterior pharynx with a tongue depressor or a cotton-tipped swab to stimulate a gag. Advance a suction catheter through the endotracheal tube to the carina to stimulate a cough.</td>
<td>Absence of both a cough and a gag is consistent with brain death.</td>
</tr>
</tbody>
</table>

CN, cranial nerve.

blood gas result documents the starting values. During the test, oxygenation can be maintained with 100% oxygen via a T-piece attached to the endotracheal tube or via a resuscitation bag such as a Mapleson device. Throughout the test, the child’s hemodynamics and oxygen saturation are monitored while the physician observes for respiratory efforts. A blood gas sample is obtained approximately 10 min into the test and every 5 min thereafter until the target pCO₂ is surpassed; ventilatory support is resumed at that time. If at any point during the test the patient becomes hypoxic or hypotensive, the test is aborted and ventilatory support is resumed. Absence of respiratory efforts with a pCO₂ ≥60 mm Hg and >20 mm Hg above baseline is consistent with brain death.

OBSERVATION PERIODS
To establish the diagnosis of brain death, the findings must remain consistent for 2 examinations separated by an observation period. Recommended observation periods are 24 hr for neonates from 37 wk gestation to term infants 30 days old, and 12 hr for infants and children older than 30 days. An observation period of 24-48 hr prior to initiation of brain death assessment is recommended following CPR or severe acute brain injury.

ANCILLARY STUDIES
Ancillary studies are not required for the diagnosis of brain death unless the clinical examination including the apnea test cannot be safely or reliably completed. Examples include cervical spinal cord injury, presence of high-therapeutic or supratherapeutic levels of sedative medications, or hemodynamic instability or desaturation during an apnea test. Ancillary studies may also be used to shorten the recommended observation period. In this case, 2 complete clinical examinations, including apnea test, should be completed and documented along with the ancillary study.

The 2 most commonly used ancillary tests are EEG and radionuclide CBF studies. A valid EEG to support suspected brain death must be performed according to accepted technical requirements, under conditions of normothermia and appropriate hemodynamics, and in the absence of drug levels sufficient to suppress the EEG response. An EEG that demonstrates electrocerebral silence over a 30 min recording time under these conditions supports the diagnosis of brain death. Advantages of this study are its wide availability and low risk. Disadvantages include potential confounders, such as artifact in the tracing and the presence of suppressing levels of drugs such as barbiturates.

A radionuclide CBF study consists of intravenous injection of a radiopharmaceutical agent followed by imaging of the brain to look for cerebral uptake. Like EEG, nuclear medicine scans are widely available and low risk. Unlike EEG, these studies are not affected by drug levels. A study that shows absence of uptake in the brain demonstrates absence of CBF and is supportive of brain death. Four-vessel intracranial contrast angiography was previously used as the definitive ancillary test, but practical technical difficulties and risks have led to the use of nuclear medicine scans instead.

Interpretation of both EEG and radionuclide CBF studies should be done by appropriately trained and qualified individuals. If the studies show electrical activity or presence of CBF, brain death cannot be declared. A 24 hr waiting period is recommended prior to repeating the clinical examination or ancillary study.

DOCUMENTATION
Documentation is an important aspect of diagnosing brain death. Complete documentation should include statements of the following:
1. Etiology and irreversibility of the coma.
2. Absence of confounding factors: hypothermia, hypotension, hypoxia, significant metabolic derangement, significant drug levels.
3. Absence of motor response to noxious stimulation.
5. Absence of respiratory effort in response to an adequate stimulus; blood gas values should be documented at the beginning and end of the apnea test.

SUPPORTIVE CARE
Following a diagnosis of brain death, supportive care may continue for hours to days as the family makes decisions about potential organ donation and comes to terms with the diagnosis. A diagnosis of brain death may not be accepted by the family for personal, religious, or
cultural reasons. It is important for care providers to be patient and supportive of the family dealing with this difficult situation.

**OBJECTIONS TO THE IDEA OF BRAIN DEATH**

Although the concept of brain death is widely accepted and very useful in facilitating organ transplantation, it is not accepted by all. Several countries do not recognize brain death, and some individuals, both medical personnel and laypeople, object to the idea of brain death.

It has been pointed out that some patients who meet brain death criteria continue to show evidence of integrative functioning, such as control over free-water homeostasis (absence of diabetes insipidus), control of temperature regulation, capacity for growth and wound healing, and variability of heart rate and blood pressure in response to stimulus. Along with scientific arguments, there are also philosophical arguments about what constitutes death and whether a person who lacks function of the brain, but not of the body, is truly dead.

*Bibliography is available at Expert Consult.*
Bibliography

Syncope is defined as a sudden transient loss of consciousness with inability to maintain postural tone. The most common cause of syncope in the normal pediatric population is neurocardiogenic syncope, also known as vasovagal syncope (Table 69-1). Although this type of syncope is very common in adolescence and has an excellent prognosis, other causes for loss of consciousness are more dangerous, thus syncope may be the first sign of more serious conditions (Table 69-2). Indeed, the occurrence of syncope may well be the pediatrician’s best opportunity to diagnose a life-threatening condition before the patient subsequently succumbs. The task of the clinician, therefore, is not only to counsel the family and the patient concerning the common form, but also to rule out a number of important life-threatening cardiac problems.

**EPIDEMIOLOGY**
Most syncope presents during adolescence, typically between 11 and 13 yr of age. The incidence is somewhat higher in girls than in boys. Approximately 25% of all young adults will have experienced at least 1 episode of neurocardiogenic syncope.

**MECHANISMS**
Syncope by whatever mechanism is caused by a lack of adequate cerebral blood flow with loss of consciousness and inability to see remain upright. The mechanisms underlying neurocardiogenic syncope are not completely understood but seem to involve some trigger event that leads to vasodilation, venous pooling in the lower part of the body, decreased cardiac filling with compensatory sinus tachycardia and sympathetic nervous system activity, and, finally, activation of cardiac C fibers leading to reflex bradycardia. The typical event is triggered by a variety of factors, such as disgust, the site of blood, other emotional reactions, particular smells, or simply prolonged standing (see Table 69-1). Most patients display a mixed picture with both blood pressure and heart rate changes. Prior to syncope, the blood pressure declines and the heart rate increases, and with loss of consciousness there is often significant bradycardia. Other patients display a principally vasopressor response with a drop in blood pressure as the most important feature. Still others primarily have a cardioinhibitory response in which sudden profound bradycardia or asystole occurs with little or no change in blood pressure prior to the event. Making the distinction between these various patterns leading

<table>
<thead>
<tr>
<th>Table 69-1</th>
<th>Noncardiac Causes of Syncope</th>
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<tbody>
<tr>
<td>Reflex vasodepressor syncope</td>
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<td>Neurocardiogenic (vasovagal)</td>
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<td>Emotion (seeing blood)</td>
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<td>Pain (needle phobia)</td>
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<td>Miscellaneous situational reflex</td>
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<td>Sneezing</td>
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<td>Exercise/post exercise</td>
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<td>Valsalva (increased intrathoracic pressure)</td>
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<td>Breath holding spells</td>
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<td>Narcolepsy/cataplexy</td>
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<td>Pulmonary embolism</td>
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<td>Ruptured ectopic pregnancy</td>
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<td>β-Blocking agents</td>
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<td>Drugs prolonging QT interval</td>
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<thead>
<tr>
<th>Table 69-2</th>
<th>Life-Threatening Cardiac Causes of Syncope</th>
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<td>Cardiomyopathies</td>
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<td>Dilated cardiomyopathy</td>
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<td>Arrhythmogenic right ventricular dysplasia</td>
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<td>Brugada syndrome</td>
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<td>Catecholaminergic polymorphic ventricular tachycardia</td>
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<td>Wolff-Parkinson-White syndrome</td>
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<td>Coronary artery anomalies</td>
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<td>Late postoperative arrhythmias</td>
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<td>Congenital or acquired complete atrioventricular block</td>
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<td>Aortic, mitral, or pulmonic valve stenosis</td>
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<td>Primary pulmonary hypertension</td>
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<td>Eisenmenger syndrome</td>
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<td>Dissecting aortic aneurysm (Marfan syndrome)</td>
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<tr>
<td>Cardiac tumor</td>
<td></td>
</tr>
</tbody>
</table>
to syncope is important for treatment considerations. In any case, with loss of consciousness and the assumption of supine posture, venous return and atrial filling dramatically increases and adequate blood pressure returns quickly.

Primary cardiac causes of syncope (see Table 69-2) include arrhythmias (see Chapter 435) such as long QT syndrome, Wolff-Parkinson-White syndrome (particularly with atrial fibrillation), ventricular tachycardia, and occasionally supraventricular tachycardia. Ventricular tachycardia may be associated with hypertrophic cardiomyopathy, repaired congenital heart disease, or a genetic cause such as catecholaminergic polymorphous ventricular tachycardia. Other arrhythmias that may lead to syncope are bradycardias such as sinus node dysfunction and high-grade 2nd or 3rd degree atrioventricular (AV) block. Patients with congenital complete AV block may present with syncope. Syncope may also be caused by cardiac obstructive lesions, such as critical aortic stenosis, or coronary artery anomalies, such as an aberrant left coronary artery arising from the right sinus of Valsalva. Finally, patients with primary pulmonary hypertension or Eisenmenger syndrome may experience syncope. In all of the obstructive forms of syncope, exercise increases the likelihood of an episode as the obstruction interferes with the ability of the heart to increased cardiac output in response to exercise.

Noncardiac causes of loss of consciousness include epilepsy, but may also include basilar artery migraine, hysterical syncope, and pseudo-seizures (see Table 69-1). Occasionally patients with narcolepsy may present as syncope. Hypoglycemia and hyperventilatation may also present with syncope.

**EVALUATION**

The most important goal in the evaluation of the new patient with syncope is to diagnose life-threatening causes of syncope so that these causes can be managed. Many patients presenting with sudden cardiac arrest caused by conditions such as long QT syndrome will have previously experienced an episode of syncope, and so the presentation with syncope is an opportunity to prevent sudden death.

The most important tool in evaluation is a careful history. The patient with neurocardiogenic syncope will be able to describe the circumstances of the event and specific prodromal symptoms. Typically, the patient will have been standing for a period of time, often on a hot day, or has gotten up suddenly from sleep or resting in a supine position. Occurrence in the shower is common, presumably caused by standing and vasodilation caused by hot water. For boys, the occurrence while urinating while standing is sometimes reported. The occurrence of syncope in girls while sitting or standing and having their hair brushed is common. Typical prodromal symptoms prior to syncope include lightheadedness, dizziness, nausea, sweating, and feeling hot or cold. Patients may report visual field changes and “rushing” in their ears. Witnesses will usually note extreme pallor or a gray color change. Injury to the patient as a result of the episode of syncope is unusual in common syncope, as the patient usually has adequate prodromal symptoms to avoid injury. Loss of consciousness is generally transient once the patient becomes supine; the loss of consciousness resolves rapidly (seconds to minutes), and there is no clear postevent state of sleepiness. Often, patients will describe other episodes with similar prodromal symptoms which did not lead to complete loss of consciousness but were aborted, often because the patient was able to assume recumbent posture. Some patients have a few tonic–clonic movements while unconscious, which resolve within seconds, and do not signify a seizure disorder.

The characteristics of cardiac syncope not due to neurocardiogenic mechanisms are generally quite different. A number of “red flags” can be identified that should lead the clinician to be suspicious that the mechanism is a life-threatening cardiac cause rather than simple fainting (Table 69-3). The occurrence during exercise suggests an arrhythmia or coronary obstruction. Injury as a result of an episode of syncope suggests sudden occurrence with a lack of adequate prodromal symp- toms, and suggests an arrhythmia. The occurrence of syncope while recumbent would be quite unusual in a patient with neurocardiogenic syncope and therefore raises the possibility of a cardiac or neurologic cause. Occasionally, a patient with syncope caused by a tachyarrhythmia will report the sensation of a racing heart prior to the event, but this is actually unusual.

A careful family history is essential in evaluation of syncope. Specifically, if there are first-degree relatives with inherited syndromes, such as a long QT syndrome or hypertrophic cardiomyopathy, this should lead to more specific evaluation of the patient. Also, if there are relatives who have died suddenly in young age without a clear and convincing cause, inherited cardiac arrhythmias or cardiomyopathies should also be suspected.

Patients with a history of heart disease, especially cardiac repair, may have causes that are specific to their repair. Sinus node dysfunction is common after the Senning or Mustard procedure for transposition of the great vessels. Ventricular tachycardia may be seen following repair of tetralogy of Fallot. A patient with a history of septal defect repair should be evaluated for the late occurrence of AV block, and patients with an implanted pacemaker should be evaluated for pacemaker lead failure.

The physical examination may also offer clues (see Table 69-3). Patients with hypertrophic cardiomyopathy may have a prominent cardiac impulse and/or an ejection murmur, as will patients with aortic stenosis. The patient with primary pulmonary hypertension will have a loud and single second heart sound and may also have an ejection click and the murmur of pulmonary insufficiency. Scars from prior cardiac surgery and pacemaker implantation would be evident.

All patients presenting with a first episode of syncope should have an electrocardiogram obtained, looking primarily for QT interval prolongation, preexcitation, ventricular hypertrophy, T-wave abnormalities, and conduction abnormalities. Other tests that may be needed depending on the results of the initial evaluation may include echocardiography, cardiac MRI, or 24-hr Holter monitoring. In patients for whom there is a strong suspicion of a paroxysmal arrhythmia, an implantable loop recorder may be the most effective means of diagnosis.

Tilt-table testing was originally developed by the military and was applied to the general population of otherwise normal individuals who have experienced syncope. While patients with neurocardiogenic syncope often will experience an episode during the tilt-table test, the test is poorly reproducible and neither particularly sensitive nor

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**Table 69-3 “Red Flags” in the Evaluation of Patients with Syncope**

| Syncope with activity or exercise or supine |
| Syncope not associated with prolonged standing |
| Syncope precipitated by loud noise or extreme emotion |
| Absence of presyncope or lightheadedness |
| Family history of syncope, drowning, sudden death, familial ventricular arrhythmia syndromes*, cardiomyopathy |
| Syncope requiring CPR |
| Injury with syncope |
| Anemia |
| Other cardiac symptoms |
| Chest pain |
| Dypsnea |
| Palpitations |
| History of cardiac surgery |
| History of Kawasaki disease |
| Implanted pacemaker |
| Abnormal physical examination |
| Murmur |
| Gallop rhythm |
| Loud and single second heart sound |
| Systolic click |
| Increased apical impulse (tachycardia) |
| Irregular rhythm |
| Hypo- or hypertension |
| Clubbing |
| Cyanosis |

*Long Qτ syndrome, Brugada syndrome, catecholamine polymorphic ventricular tachycardia, arrhythmogenic right ventricular dysplasia.
specific. The use of tilt-table testing for the otherwise normal adolescent with simple fainting is discouraged. Some pediatric cardiologists still employ the test in severely affected individuals who are not responding to standard therapy, as a way of planning more aggressive therapy.

Additional tests to look for anemia, hypoglycemia, drugs of abuse, and other etiologies noted in Table 69-1 will be determined by the history and physical exam.

**TREATMENT**

Most patients with neurocardiogenic syncope will experience eventual resolution by adulthood; many even get better spontaneously within a few months or years. Many therapies have been employed for this condition, but it is difficult to determine which ones are truly effective because of the lack of randomized prospective studies. Nonetheless, initial salt and water supplementation is commonly recommended, particularly in those who have a low-salt diet or who have limited their fluid intake. A reasonable second step is treatment with fludrocortisone, a mineralocorticoid that promotes sodium and water retention with potassium loss. In patients who have a prominent low-blood-pressure response, the α-agonist midodrine may be useful. Both midodrine and fludrocortisone should be managed with careful monitoring of the supine blood pressure, as they may lead to supine hypertension. Some have advocated the use of β blockers such as, pindolol, which offers some advantages because of its intrinsic sympathomimetic activity; randomized prospective trials have not supported the effectiveness of beta blockers. Occasionally, the use of selective serotonin reuptake inhibitors is effective in certain patients.Occasional patients who present with profound bradycardia or asystole can be helped by implantation of a dual-chamber transvenous pacemaker with programmed hysteresis (rapid pacing in response to a sudden drop in heart rate).

The most important therapeutic step is educational. Once the young patient is aware of the importance of the prodromal symptoms, they can take appropriate steps to change position and not attempt to remain standing. In many, this is all that is necessary to adequately manage their symptoms.

*Bibliography is available at Expert Consult.*

### 69.1 Disorders of Orthostatic Intolerance

*George F. Van Hare*

Postural orthostatic tachycardia syndrome (POTS) is a female-predominant condition in which the patient experiences an impressive and symptomatic elevation in heart rate on standing. This orthostatic intolerance disorder manifests with presyncopal symptoms, lightheadedness, dizziness, palpitations, leg weakness and tremulousness on standing. An orthostatic heart rate of >120 beats/min and a rise in heart rate of ≥30 beats/min with 5 min of standing suggest the diagnosis. This should not be confused with neurocardiogenic syncope. Patients with POTS often also complain of other symptoms, such as fatigue, chest pain, headaches, abdominal pain, bloating, nausea, emesis, sleep disturbances, and fatigue. There is an overlap with patients with POTS and chronic fatigue syndrome or functional gastrointestinal disorders. Many patients are evaluated in dysautonomia programs and may have evidence of a small fiber polyneuropathy. Treatment of POTS is symptomatic and often not particularly successful. The use of β blockers may be effective; some physicians have advised increase physical activity through cardiac rehabilitation.

Juvenile-onset widespread pain syndromes associated with a small fiber polyneuropathy (dysautonomia) have associated gastrointestinal, cardiovascular, fatigue, headache symptoms as well as erythromelalgia. Steroids or intravenous immunoglobulin has been used to treat this disorder.

*Bibliography is available at Expert Consult.*
Bibliography
Bibliography
Shock is an acute process characterized by the body’s inability to deliver adequate oxygen to meet the metabolic demands of vital organs and tissues. Insufficient oxygen at the tissue level is unable to support normal aerobic cellular metabolism, resulting in a shift to less-efficient anaerobic metabolism. As shock progresses, increases in tissue oxygen extraction are unable to compensate for this deficiency in oxygen delivery, leading to progressive clinical deterioration and lactic acidosis. If inadequate tissue perfusion persists, adverse vascular, inflammatory, metabolic, cellular, endocrine, and systemic responses worsen physiologic instability.

Compensation for inadequate oxygen delivery involves a complex set of responses that attempt to preserve oxygenation of the vital organs (i.e., brain, heart, kidneys, liver) at the expense of other organs (i.e., skin, gastrointestinal tract, muscles). Of importance, the brain is especially sensitive to periods of poor oxygen supply, given its lack of capacity for anaerobic metabolism. Initially, shock is often well compensated, but it may rapidly progress to an uncompensated state requiring more aggressive therapies to achieve clinical recovery or improvement. The combination of a continued presence of an inciting trigger and the body’s exaggerated and potentially harmful neurohumoral, inflammatory, and cellular responses leads to the progression of shock. Irrespective of the underlying cause of shock, the specific pattern of response, pathophysiology, clinical manifestations, and treatments may vary significantly, depending on the specific etiology (which may be unknown), the clinical circumstances, and an individual patient’s biologic response to the shock state. Untreated shock causes irreversible tissue and organ injury (i.e., irreversible shock) and, ultimately, death.

**EPIDEMIOLOGY**

Shock occurs in approximately 2% of all hospitalized infants, children, and adults in developed countries, and the mortality rate varies substantially depending on the etiology and clinical circumstances. Most patients who do not survive, do not die in the acute hypotensive phase of shock, but rather as a result of associated complications and multiple organ dysfunction syndrome (MODS). MODS is defined as any alteration of organ function that requires medical support for maintenance, and the presence of MODS in patients with shock substantially increases the probability of death. In pediatrics, educational efforts and the utilization of standardized management guidelines that emphasize early recognition and intervention along with the rapid transfer of critically ill patients to a pediatric intensive care unit have led to decreases in the mortality rate for shock (Fig. 70-1).

**DEFINITION**

Shock classification systems generally define 5 major types of shock: hypovolemic, cardiogenic, distributive, obstructive, and septic (Table 70-1). **Hypovolemic shock**, the most common cause of shock in children worldwide, is most frequently caused by diarrhea, vomiting, or hemorrhage. **Cardiogenic shock** is seen in patients with either congenital heart disease (before or after surgery, including heart transplantation) or with congenital or acquired cardiomyopathies, including acute myocarditis. **Obstructive shock** stems from any lesion that creates a mechanical barrier that impedes adequate cardiac output, which include pericardial tamponade, tension pneumothorax, pulmonary embolism, and ductus-dependent congenital heart lesions. **Distributive shock** is caused by inadequate vasomotor tone, which leads to capillary leak and maldistribution of fluid into the interstitium. **Septic shock** is often discussed synonymously with distributive shock, but the septic process usually involves a more complex interaction of distributive, hypovolemic, and cardiogenic shock.
Chapter 70 • Shock

**Pathophysiology**

An initial insult triggers shock, leading to inadequate oxygen delivery to organs and tissues. Compensatory mechanisms attempt to maintain blood pressure by increasing cardiac output and systemic vascular resistance (SVR). The body also attempts to optimize oxygen delivery to the tissues by increasing oxygen extraction and redistributing blood flow to the brain, heart, and kidneys at the expense of the skin and gastrointestinal tract. These responses lead to an initial state of compensated shock, in which blood pressure is maintained. If treatment is not initiated or is inadequate during this period, decompensated shock develops, with hypotension and tissue damage that may lead to multisystem organ dysfunction and ultimately death (Fig. 70-2, Tables 70-2 and 70-3).

In the early phases of shock, multiple compensatory physiologic mechanisms act to maintain blood pressure and preserve tissue perfusion and oxygen delivery. Cardiovascular effects include increases in heart rate, stroke volume, and vascular smooth muscle tone, which are regulated through sympathetic nervous system activation and
The Types of Shock

**HYPOVOLEMIC**
- Decreased preload secondary to internal or external losses

**CARDIOGENIC**
- Cardiac pump failure secondary to poor myocardial function

**DISTRIBUTIVE**
- Abnormalities of vasomotor tone from loss of venous and arterial capacitance

**SEPTIC**
- Encompasses multiple forms of shock
  - Hypovolemic: third spacing of fluids into the extracellular, interstitial space
  - Distributive: early shock with decreased afterload
  - Cardiogenic: depression of myocardial function by endotoxins

**OBSERVABLE**
- Decreased cardiac output secondary to direct impediment to right- or left-heart outflow or restriction of all cardiac chambers

**POTENTIAL ETIOLOGIES**
- Blood loss: hemorrhage, plasma loss: burns, nephrotic syndrome, water/electrolyte loss: vomiting, diarrhea
- Congenital heart disease: Cardiomyopathies: infectious or acquired, dilated or restrictive
- Anaphylaxis: Neurologic: loss of sympathetic vascular tone secondary to spinal cord or brainstem injury
- Bacterial: Viral
- Fungal
- Drugs
- Tension pneumothorax
- Pericardial tamponade
- Pulmonary embolism
- Anterior mediastinal masses
- Critical coarctation of the aorta

**Table 70-1** Types of Shock

<table>
<thead>
<tr>
<th>HYPOVOLEMIC</th>
<th>CARDIOGENIC</th>
<th>DISTRIBUTIVE</th>
<th>SEPTIC</th>
<th>OBSTRUCTIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased preload secondary to internal or external losses</td>
<td>Cardiac pump failure secondary to poor myocardial function</td>
<td>Abnormalities of vasomotor tone from loss of venous and arterial capacitance</td>
<td>Encompasses multiple forms of shock</td>
<td>Decreased cardiac output secondary to direct impediment to right- or left-heart outflow or restriction of all cardiac chambers</td>
</tr>
</tbody>
</table>

**Algoithm**

**Initial insult**

Triggers shock

Decreased perfusion

Body’s compensatory mechanisms

**Compensated shock**

**Decompensated shock**

**Tissue damage**

**Multisystem organ failure**

**Death**

**Figure 70-2** Algorithm for decompensated shock.

CO₂ production from poor tissue perfusion. Renal excretion of hydro-
via several mechanisms, with changes in heart rate, preload, afterload,
and myocardial contractility occurring separately or in combination
(Table 70-4). Hypovolemic shock is characterized primarily by fluid loss and decreased preload. Tachycardia and an increase in SVR are
the initial compensatory responses to maintain cardiac output and
systemic blood pressure. Without adequate volume replacement, hypo-
tension develops, followed by tissue ischemia and further clinical dete-
roration. When there is preexisting low plasma oncotic pressure
(casted by nephrotic syndrome, malnutrition, hepatic dysfunction,
acute severe burns, etc.), even further volume loss and exacerbation of
shock may occur because of endothelial breakdown and worsening
capillary leak.

In contrast, the underlying pathophysiologic mechanism leading to
distributive shock is a state of abnormal vasodilation and decreased
SVR. Sepsis, hypoxia, poisonings, anaphylaxis, spinal cord injury, or
mitochondrial dysfunction can cause vasodilatory shock (Fig. 70-3).
The lowering of SVR is accompanied initially by a maldistribution of
blood flow away from vital organs and a compensatory increase in
cardiac output. This process leads to significant decreases in both preload and afterload. Therapies for distributive shock must address
both of these problems simultaneously.

Cardiogenic shock may be seen in patients with myocarditis, car-
diomyopathy, congenital heart disease, or arrhythmias, or following
cardiac surgery (see Chapter 434). In these instances, myocardial con-
tractility is affected, leading to systolic and/or diastolic dysfunction.
The later phases of all forms of shock frequently have a negative impact
on the myocardium, leading to development of a cardiogenic compo-
nent to the shock state.

Septic shock is often a unique combination of distributive, hypovo-
lemic, and cardiogenic shock. Hypovolemia from intravascular fluid
losses occurs through capillary leak. Cardiogenic shock results from
the myocardial-depressant effects of sepsis, and distributive shock is
the result of decreased SVR. The degree to which a patient exhibits
each of these responses varies, but there are frequently alterations in
preload, afterload, and myocardial contractility.

In septic shock, it is important to distinguish between the inciting
infection and the host inflammatory response. Normally, host immu-
nity prevents the development of sepsis via activation of the reticular
endothelial system along with the cellular and humoral immune
systems. This host immune response produces an inflammatory
cascade of toxic mediators, including hormones, cytokines, and
enzymes. If this inflammatory cascade is uncontrolled, derangement of
the microcirculatory system leads to subsequent organ and cellular
dysfunction.

The systemic inflammatory response syndrome (SIRS) is an
inflammatory cascade that is initiated by the host response to an
Infectious or noninfectious trigger (Table 70-5). This inflammatory cascade is triggered when the host defense system does not adequately recognize and/or clear the triggering event. The inflammatory cascade initiated by shock can lead to hypovolemia, cardiac and vascular failure, acute respiratory distress syndrome (ARDS), insulin resistance, decreased cytochrome P450 activity (decreased steroid synthesis), coagulopathy, and unresolved or secondary infection. Tumor necrosis factor (TNF) and other inflammatory mediators increase vascular permeability, causing diffuse capillary leak, decreased vascular tone, and an imbalance between perfusion and metabolic demands of the tissues. TNF and interleukin (IL)-1 stimulate the release of proinflammatory and antiinflammatory mediators, causing fever and vasodilation. Proinflammatory mediators include IL-6, IL-12, interferon-γ, and macrophage migration inhibitory factor; antiinflammatory cytokines include IL-10, transforming growth factor-β, and IL-4. Arachidonic acid metabolites lead to the development of fever, tachypnea, ventilation-perfusion abnormalities, and lactic acidosis. Nitric oxide, released from the endothelium or inflammatory cells, is a major contributor to hypotension. Myocardial depression is caused directly by myocardial-depressant factors, TNF, and some interleukins, and further depressed via depleted catecholamines, increased β-endorphin, and production of myocardial nitric oxide.

The inflammatory cascade (Fig. 70-4) is initiated by toxins or superantigens via macrophage binding or lymphocyte activation. The vascular endothelium is both a target of tissue injury and a source of inflammatory mediators. The release of these mediators leads to an imbalance between perfusion and metabolic demands of the tissues. This imbalance results in the development of organ dysfunction, which can be assessed by a variety of criteria.

### Table 70-2 Criteria for Organ Dysfunction

<table>
<thead>
<tr>
<th>ORGAN SYSTEM</th>
<th>CRITERIA FOR DYSFUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Despite administration of isotonic intravenous fluid bolus ≥60 mL/kg in 1 hr; decrease in BP (hypotension) systolic BP &lt;90 mm Hg, mean arterial pressure &lt;70 mm Hg, &lt;5th percentile for age, or systolic BP &lt;2 SD below normal for age or Need for vasoactive drug to maintain BP in normal range (dopamine &gt;5 µg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose) or Two of the following: Unexplained metabolic acidosis: base deficit &gt;5.0 mEq/L Increased arterial lactate: &gt;1 mmol/Liter or &gt;2x upper limit of normal Oliguria: urine output &lt;0.5 mL/kg/hr Prolonged capillary refill: &gt;5 sec Core to peripheral temperature gap &gt;3°C (5.4°F)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>PaO2/FIO2 ratio &lt;300 in absence of cyanotic heart disease or preexisting lung disease or PaCO2 &gt;65 torr or 20 mm Hg over baseline PaCO2 or Need for &gt;50% FIO2 to maintain saturation ≥92% or Need for nonelective invasive or noninvasive mechanical ventilation</td>
</tr>
<tr>
<td>Neurologic</td>
<td>GCS score ≤11 or Acute change in mental status with a decrease in GCS score ≥3 points from abnormal baseline</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Platelet count &lt;100,000/mm³ or a decline of 50% in the platelet count from the highest value recorded over the last 3 days (for patients with chronic hematologic or oncologic disorders) or INR &gt;1.5 or Activated prothrombin time &gt;60 sec</td>
</tr>
<tr>
<td>Renal</td>
<td>Serum creatinine &gt;0.5 mg/dL, ≥2x upper limit of normal for age, or 2-fold increase in baseline creatinine value</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Total bilirubin ≥4 mg/dL (not applicable for newborn) Alkaline transaminase level 2x upper limit of normal for age</td>
</tr>
</tbody>
</table>

BP: blood pressure; FIO2, fraction of inspired oxygen; GCS, Glasgow Coma Scale; INR, international normalized ratio; Pa CO2, arterial partial pressure of carbon dioxide; PaO2, partial pressure arterial oxygen.

### Table 70-3 Signs of Decreased Perfusion

<table>
<thead>
<tr>
<th>ORGAN SYSTEM</th>
<th>↓ PERFUSION</th>
<th>↓↓ PERFUSION</th>
<th>↓↓↓ PERFUSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td>—</td>
<td>Restless, apathetic, anxious</td>
<td>Agitated/confused, stuporous, coma</td>
</tr>
<tr>
<td>Respiration</td>
<td>—</td>
<td>↑ Ventilation</td>
<td>↑↑ Ventilation</td>
</tr>
<tr>
<td>Metabolism</td>
<td>—</td>
<td>Compensated metabolic acidemia</td>
<td>Uncompensated metabolic acidemia</td>
</tr>
<tr>
<td>Gut</td>
<td>—</td>
<td>↓ Motility</td>
<td>Ileus</td>
</tr>
<tr>
<td>Kidney</td>
<td>↓ Urine volume ↑ Urinary specific gravity</td>
<td>Oliguria (&lt;0.5 mL/kg/hr)</td>
<td>Oliguria/anuria</td>
</tr>
<tr>
<td>Skin</td>
<td>Delayed capillary refill</td>
<td>Cool extremities</td>
<td>Mottled, cyanotic, cold extremities</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>↑ Heart rate</td>
<td>↑↑ Heart rate ↓ Peripheral pulses</td>
<td>↑↑ Heart rate ↓ Blood pressure, central pulses only</td>
</tr>
</tbody>
</table>

EXTRACORPOREAL FLUID LOSS
Hypovolemic shock may be a result of direct blood loss through hemorrhage or abnormal loss of body fluids (diarrhea, vomiting, burns, diabetes mellitus or insipidus, nephrosis)

LOWER PLASMA Oncotic FORCES
Hypovolemic shock may also result from hypoproteinemia (liver injury, or as a progressive complication of increased capillary permeability)

ABNORMAL VASODILATION
Distributive shock (neurogenic, anaphylaxis, or septic shock) occurs when there is loss of vascular tone—venous, arterial, or both (sympathetic blockade, local substances affecting permeability, acidosis, drug effects, spinal cord transection)

INCREASED VASCULAR PERMEABILITY
Sepsis may change the capillary permeability in the absence of any change in capillary hydrostatic pressure (endotoxins from sepsis, excess histamine release in anaphylaxis)

CARDIAC DYSFUNCTION
Peripheral hypoperfusion may result from any condition that affects the heart's ability to pump blood efficiently (ischemia, acidosis, drugs, constrictive pericarditis, pancreatitis, sepsis)
of mediators that may cause further injury. Biochemical responses include the production of arachidonic acid metabolites, release of myocardial depressant factors, release of endogenous opiates, activation of the complement system, as well as the production and release of many other mediators, which may be either proinflammatory or antiinflammatory. The balance between these mediator groups for an individual patient contributes to the progression of disease and affects the chance for survival.

**CLINICAL MANIFESTATIONS**

Table 70-1 shows a classification system for shock. Categorization is important, but there may be significant overlap among these groups, especially in septic shock. The clinical presentation of shock depends in part on the underlying etiology, but if unrecognized and untreated, all forms of shock follow a common and untoward progression of clinical signs and pathophysiologic changes that may ultimately lead to irreversible organ injury and death (see Fig. 70-2).

Shock may initially manifest as only tachycardia, with or without tachypnea. Progression leads to decreased urine output, poor peripheral perfusion, respiratory distress or failure, alteration of mental status, and low blood pressure (see Table 70-3). A significant misconception is that shock occurs only with low blood pressure; hypotension is often a late finding and is not a criterion for the diagnosis of shock because of a complex set of compensatory mechanisms attempting to preserve blood pressure. Hypotension reflects an advanced state of decompensated shock and is associated with increased morbidity and mortality.

**Hypovolemic shock** often manifests initially as orthostatic hypotension and is associated with dry mucous membranes, dry axillae, poor skin turgor, and decreased urine output. Depending on the degree of dehydration, the patient with hypovolemic shock may present with either normal or slightly cool distal extremities, and pulses may be normal, decreased, or absent depending on disease severity. The presenting signs of **cardiogenic shock** are tachycardia, cool extremities, delayed capillary filling time, poor peripheral and/or central pulses, declining mental status, and decreased urine output, caused by the combination of decreased cardiac output and compensatory peripheral

**Table 70-5** Differential Diagnosis of Systemic Inflammatory Response Syndrome

| INFECTION |  
| Bacteremia or meningitis (Streptococcus pneumoniae, Haemophilus influenzae type b, Neisseria meningitidis, group A streptococcus, Staphylococcus aureus)  
| Viral illness (influenza, enteroviruses, hemorrhagic fever group, herpes simplex virus, respiratory syncytial virus, cytomegalovirus, Epstein-Barr virus)  
| Encephalitis (arboviruses, enteroviruses, herpes simplex virus)  
| Ricketsiae (Rocky Mountain spotted fever, Ehrlichia, Q fever)  
| Syphilis  
| Vaccine reaction (pertussis, influenza, measles)  
| Toxin-mediated reaction (toxic shock, staphylococcal scalded skin syndrome)  
|  
| CARDIOPULMONARY |  
| Pneumonia (bacteria, virus, mycobacteria, fungi, allergic reaction)  
| Pulmonary emboli  
| Heart failure  
| Arrhythmia  
| Pericarditis  
| Myocarditis  
|  
| METABOLIC-ENDOCRINE |  
| Adrenal insufficiency (adrenogenital syndrome, Addison disease, corticosteroid withdrawal)  
| Electrolyte disturbances (hyponatremia or hypernatremia; hypocalcemia or hypercalcemia)  
| Diabetes insipidus  
| Diabetes mellitus  
| Inborn errors of metabolism (organic acidosis, urea cycle, carnitine deficiency, mitochondrial disorders)  
| Hypoglycemia  
| Rye syndrome  
|  
| GASTROINTESTINAL |  
| Gastroenteritis with dehydration  
| Volvulus  
| Intussusception  
| Appendicitis  
| Peritonitis (spontaneous, associated with perforation or peritoneal dialysis)  
| Necrotizing enterocolitis  
| Hepatitis  
| Hemorrhage  
| Pancreatitis  
|  
| HEMATOLOGIC |  
| Anemia (sickle cell disease, blood loss, nutritional)  
| Methemoglobinemia  
| Splenectomy or sequestration crisis  
| Leukemia or lymphoma  
| Hemophagocytic syndromes  
|  
| NEUROLOGIC |  
| Intoxication (drugs, carbon monoxide, intentional or accidental overdose)  
| Intracranial hemorrhage  
| Infant botulism  
| Trauma (child abuse, accidental)  
| Guillain-Barré syndrome  
| Myasthenia gravis  
|  
| OTHER |  
| Anaphylaxis (food, drug, insect sting)  
| Hemolytic-uremic syndrome  
| Kawasaki disease  
| Erythema multiforme  
| Hemorrhagic shock–encephalopathy syndrome  
| Poisoning  
| Toxic envenomation  
| Macrophage activation syndrome  

---

**Figure 70-3** Mechanisms of vasodilatory shock. Septic shock and states of prolonged shock causing tissue hypoxia with lactic acidosis increase nitric oxide synthesis, activate the adenosine triphosphate (ATP)–sensitive and calcium-regulated potassium channels (K$_{ATP}$ and K$_{Ca}$, respectively) in vascular smooth muscle, and lead to depletion of vasopressin. cGMP, cyclic guanosine monophosphate. (From Landry DW, Oliver JA: The pathogenesis of vasodilatory shock, N Engl J Med 345:588-595, 2001.)
Further deterioration leads to septic shock (severe sepsis plus the persistence of hypoperfusion or hypotension despite adequate fluid resuscitation or a requirement for vasoactive agents), MODS, and possibly death (Table 70-7). This is a complex spectrum of clinical problems that is a leading cause of mortality in children worldwide. This mortality can be mitigated and outcomes improved with early recognition and treatment.

Obstructive shock often also manifests as inadequate cardiac output because of a physical restriction of forward blood flow, and the acute presentation may quickly progress to cardiac arrest. Distributive shock manifests initially as peripheral vasodilation and increased but inadequate cardiac output. Regardless of etiology, uncompensated shock, with hypotension, high SVR, decreased cardiac output, respiratory failure, obtundation, and oliguria, occurs late in the progression of disease. Table 70-6 lists the hemodynamic findings in various shock states. Additional clinical findings in shock include cutaneous lesions such as petechiae, diffuse erythema, ecchymoses, ecthyma gangrenosum, and peripheral gangrene. Jaundice can be present either as a sign of infection or as a result of MODS.

Sepsis is defined as SIRS resulting from a suspected or proven infectious etiology. The clinical spectrum of sepsis begins when a systemic (e.g., bacteremia, rickettsial disease, fungemia, viremia) or localized (e.g., meningitis, pneumonia, pyelonephritis) infection progresses from sepsis to severe sepsis (the presence of sepsis combined with organ dysfunction). Further deterioration leads to septic shock (severe sepsis plus the persistence of hypoperfusion or hypotension despite adequate fluid resuscitation or a requirement for vasoactive agents), MODS, and possibly death (Table 70-7). This is a complex spectrum of clinical problems that is a leading cause of mortality in children worldwide. This mortality can be mitigated and outcomes improved with early recognition and treatment.

Although septic shock is primarily distributive in nature, multiple other elements of pathophysiology are represented in this disease process. The initial signs and symptoms of sepsis include alterations in temperature regulation (hyperthermia or hypothermia), tachycardia, and tachypnea. In the early stages (hyperdynamic phase, low SVR, or “warm” shock), cardiac output increases in an attempt to maintain adequate oxygen delivery and meet the greater metabolic demands of the organs and tissues. As septic shock progresses, cardiac output falls in response to the effects of numerous inflammatory mediators, leading to a compensatory elevation in SVR and the development of “cold” shock.
The Acutely Ill Child

incubation of cultures, and results often are not positive. Additional evidence for identifying an infectious etiology as the cause of SIRS includes physical examination findings, imaging, presence of white blood cells in normally sterile body fluids, and suggestive rashes such as petechiae and purpura. Affected children should be admitted to an intensive care unit or other highly monitored environment, as indicated by clinical status and the resources of the medical facility. These patients necessitate continuous monitoring, with a combination of

**DIAGNOSIS**

Shock is a clinical diagnosis based on a thorough history and physical examination (see Tables 70-2 and 70-3). Of note, septic shock has a specific consensus conference definition (see Table 70-7). In cases of suspected septic shock, an infectious etiology should be sought through culture of clinically appropriate specimens and prompt initiation of empiric antimicrobial therapy based on patient age, underlying disease, and geographic location, recognizing that time is necessary for

### Table 70-6 Hemodynamic Variables in Different Shock States

<table>
<thead>
<tr>
<th>TYPE OF SHOCK</th>
<th>CARDIAC OUTPUT</th>
<th>SYSTEMIC VASCULAR RESISTANCE</th>
<th>MEAN ARTERIAL PRESSURE</th>
<th>CAPILLARY WEDGE PRESSURE</th>
<th>CENTRAL VENOUS PRESSURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemic</td>
<td>↓</td>
<td>↑</td>
<td>↔ or ↓</td>
<td>↓↓↓</td>
<td>↓↓↓</td>
</tr>
<tr>
<td>Cardiogenic*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>←</td>
<td>↑</td>
<td>↔ or ↓</td>
<td>↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Diastolic</td>
<td>↑↓</td>
<td>↑↑</td>
<td>↔</td>
<td>↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Obstructive</td>
<td>↑</td>
<td>↑</td>
<td>↔ or ↓</td>
<td>↑↑↑†</td>
<td>↑↑↑†</td>
</tr>
<tr>
<td>Distributive</td>
<td>↑↑</td>
<td>↓↓↓</td>
<td>↔ or ↓</td>
<td>↑</td>
<td>↑ or ←</td>
</tr>
<tr>
<td>Septic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>↑↑↑</td>
<td>↓↓↓</td>
<td>↔ or ↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Late</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓</td>
<td>↑</td>
<td>↑ or ←</td>
</tr>
</tbody>
</table>

*Systolic or diastolic dysfunction.
†Wedge pressure, central venous pressure, and pulmonary artery diastolic pressures are equal.
‡Wide pulse pressure.

### Table 70-7 International Consensus Definitions for Pediatric Sepsis

<table>
<thead>
<tr>
<th>Infection</th>
<th>Suspected or proven infection or a clinical syndrome associated with high probability of infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIRS</td>
<td>Two of 4 criteria, 1 of which must be abnormal temperature or abnormal leukocyte count:</td>
</tr>
<tr>
<td></td>
<td>1. Core temperature &gt;38.5°C (101.3°F) or &lt;36°C (96.8°F) (rectal, bladder, oral, or central catheter)</td>
</tr>
<tr>
<td></td>
<td>2. Tachycardia:</td>
</tr>
<tr>
<td></td>
<td>Mean heart rate &gt;2 SD above normal for age in absence of external stimuli, chronic drugs or painful stimuli or</td>
</tr>
<tr>
<td></td>
<td>Unexplained persistent elevation over 0.5-4 hr or</td>
</tr>
<tr>
<td></td>
<td>In children &lt;1 yr old, persistent bradycardia over 0.5 hr (mean heart rate &lt;10th percentile for age in absence of vagal stimuli, β-blocker drugs, or congenital heart disease)</td>
</tr>
<tr>
<td></td>
<td>3. Respiratory rate &gt;2 SD above normal for age or acute need for mechanical ventilation not related to neuromuscular disease or general anestheisa</td>
</tr>
<tr>
<td></td>
<td>4. Leukocyte count elevated or depressed for age (not secondary to chemotherapy) or &gt;10% immature neutrophils</td>
</tr>
<tr>
<td>Sepsis</td>
<td>SIRS plus a suspected or proven infection</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>Sepsis plus 1 of the following:</td>
</tr>
<tr>
<td></td>
<td>1. Cardiovascular organ dysfunction, defined as:</td>
</tr>
<tr>
<td></td>
<td>• Hypotension &lt;5th percentile for age or systolic blood pressure &lt;2 SD below normal for age or</td>
</tr>
<tr>
<td></td>
<td>• Need for vasoactive drug to maintain blood pressure</td>
</tr>
<tr>
<td></td>
<td>or</td>
</tr>
<tr>
<td></td>
<td>• 2 of the following:</td>
</tr>
<tr>
<td></td>
<td>• Unexplained metabolic acidosis: base deficit &gt;5 mEq/L</td>
</tr>
<tr>
<td></td>
<td>• Increased arterial lactate: &gt;2 times upper limit of normal</td>
</tr>
<tr>
<td></td>
<td>• Oliguria: urine output &lt;0.5 mL/kg/hr</td>
</tr>
<tr>
<td></td>
<td>• Prolonged capillary refill: &gt;5 sec</td>
</tr>
<tr>
<td></td>
<td>• Core to peripheral temperature gap ≥3°C (5.4°F)</td>
</tr>
<tr>
<td></td>
<td>2. ARDS as defined by the presence of a PaO₂/FIO₂ ratio ≤300 mm Hg, bilateral infiltrates on chest radiograph, and no evidence of left heart failure or</td>
</tr>
<tr>
<td></td>
<td>Sepsis plus 2 or more organ dysfunctions (respiratory, renal, neurologic, hematologic, or hepatic)</td>
</tr>
<tr>
<td>Septic shock</td>
<td>Sepsis plus cardiovascular organ dysfunction as defined above</td>
</tr>
<tr>
<td>MODS</td>
<td>Presence of altered organ function such that homeostasis cannot be maintained without medical intervention</td>
</tr>
</tbody>
</table>

FIO₂, fraction of inspired oxygen; PaO₂, partial pressure arterial oxygen.
noninvasive (pulse oximetry, capnography, near infra-red spectroscopy) and invasive (central venous pressure, arterial blood pressure) techniques as clinically indicated.

**LABORATORY FINDINGS**

Laboratory findings often include evidence of hematologic abnormalities and electrolyte disturbances. Hematologic abnormalities may include thrombocytopenia, prolonged prothrombin and partial thromboplastin times, reduced serum fibrinogen level, elevations of fibrin split products, and anemia. Elevated neutrophil counts and increased immature forms (i.e., bands, myelocytes, promyelocytes), vacuolation of neutrophils, toxic granulations, and Döhle bodies can be seen with infection. Neutropenia or leukopenia may be an ominous sign of overwhelming sepsis.

Glucose dysregulation, a common stress response, may manifest as hyperglycemia or hypoglycemia. Other electrolyte abnormalities are hypocalcemia, hypoalbuminemia, and metabolic acidosis. Renal and/or hepatic function may also be abnormal. Patients with ARDS or pneumonia have impairment of oxygenation (decreased partial pressure arterial oxygen \([Pao_2]\)) as well as of ventilation (increased arterial partial pressure of carbon dioxide \([Paco_2]\)) in the later stages of lung injury (see Chapter 71).

The hallmark of uncompensated shock is an imbalance between oxygen delivery \((Do_2)\) and oxygen consumption \((Vo_2)\). Oxygen delivery normally exceeds oxygen consumption threefold. The oxygen extraction ratio is approximately 25%, thus producing a normal mixed venous oxygen saturation \((SV_o_2)\) of 75-80%. A falling \(SV_o_2\) value, as measured by cooximetry, reflects an increasing oxygen extraction ratio and documents a decrease in oxygen delivery relative to consumption. This increase in oxygen extraction by the end-organs is an attempt to maintain adequate oxygen delivery at the cellular level. This state is manifested clinically by increased lactic acid production (high anion gap, metabolic acidosis) caused by anaerobic metabolism and the compensatory increase in tissue oxygen extraction. The gold standard measurement of \(SV_o_2\) is from a pulmonary arterial catheter, but measurements from this location are often not clinically feasible. Sites such as the right ventricle, right atrium, superior vena cava \((SVCO_2)\), or inferior vena cava are often used as surrogate measures of mixed venous blood to follow the adequacy of oxygen delivery and effectiveness of therapeutic interventions. Elevated blood lactate levels reflect poor tissue oxygen delivery noted in all forms of shock.

**TREATMENT**

**Initial Management**

Early recognition and prompt intervention are extremely important in the management of all forms of shock (Tables 70-8 to 70-12). The vital sign targets and dose recommendations in Tables 70-9 to 70-11 should be adjusted to pediatric-size patients. Baseline mortality is much lower in pediatric shock than in adult shock, and further improvements in mortality are associated with early interventions (see Fig. 70-1). The initial assessment and treatment of the pediatric shock patient should include stabilization of airway, breathing, and circulation as established by the American Heart Association’s pediatric advanced life support and neonatal advanced life support guidelines (see Chapter 67). Depending on the severity of shock, further airway intervention, including intubation and mechanical ventilation, may be necessary to lessen the work of breathing and decrease the body’s overall metabolic demands.

Given the predominance of sepsis and hypovolemia as the most common causes of shock in the pediatric population, most therapeutic regimens are based on guidelines established in these settings. Immediately following establishment of intravenous (IV) or intraosseous...
Table 70-9 Recommendations: Initial Resuscitation and Infection Issues—Adults

INITIAL RESUSCITATION

1. Protocolized, quantitative resuscitation of patients with sepsis-induced tissue hypoperfusion (defined in this document as hypotension persisting after initial fluid challenge or blood lactate concentration ≥4 mmol/L). Goals during the 1st 6 hr of resuscitation:
   (a) Central venous pressure 8-12 mm Hg
   (b) Mean arterial pressure (MAP) ≥65 mm Hg
   (c) Urine output ≥0.5 mL kg⁻¹ hr⁻¹
   (d) Central venous (superior vena cava) or mixed venous oxygen saturation 70% or 65%, respectively
2. In patients with elevated lactate levels, targeting resuscitation to normalize lactate as rapidly as possible.

SCREENING FOR SEPSIS AND PERFORMANCE IMPROVEMENT

1. Routine screening of potentially infected seriously ill patients for severe sepsis to allow earlier implementation of therapy.
2. Hospital-based performance improvement efforts in severe sepsis.

DIAGNOSIS

1. Cultures as clinically appropriate before antimicrobial therapy if no significant delay (>45 min) in the start of antimicrobial(s). At least 2 sets of blood cultures (both aerobic and anaerobic bottles) be obtained before antimicrobial therapy with at least 1 drawn percutaneously and 1 drawn through each vascular access device, unless the device was recently (<48 hr) inserted.
2. Use of the 1,3 β-D-glucan assay, mannan and antimannan antibody assays, if available and invasive candidiasis is in differential diagnosis of cause of infection.
3. Imaging studies performed promptly to confirm a potential source of infection.

ANTIMICROBIAL THERAPY

1. Administration of effective intravenous antimicrobials within the first hour of recognition of septic shock and severe sepsis without septic shock as the goal of therapy.
2a. Initial empiric antinfecive therapy of one or more drugs that have activity against all likely pathogens (bacterial and/or fungal and/or viral) and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis.
2b. Antimicrobial regimen should be reassessed daily for potential deescalation.
3. Use of low procalcitonin levels or similar biomarkers to assist the clinician in the discontinuation of empiric antibiotics in patients who initially appeared septic, but have no subsequent evidence of infection.
4a. Combination empirical therapy for neutropenic patients with severe sepsis and for patients with difficult to treat, multidrug-resistant bacterial pathogens such as Acinetobacter and Pseudomonas spp.
4b. Empiric combination therapy should not be administered for more than 3-5 days. Deescalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known.
5. Duration of therapy typically 7-10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with Staphylococcus aureus; some fungal and viral infections or immunologic deficiencies, including neutropenia.
6. Antiviral therapy initiated as early as possible in patients with severe sepsis or septic shock of viral origin.
7. Antimicrobial agents should not be used in patients with severe inflammatory states determined to be of noninfectious cause.

SOURCE CONTROL

1. A specific anatomical diagnosis of infection requiring consideration for emergent source control be sought and diagnosed or excluded as rapidly as possible, and intervention be undertaken for source control within the 1st 12 hr after the diagnosis is made, if feasible.
2. When infected peripancreatic necrosis is identified as a potential source of infection, definitive intervention is best delayed until adequate demarcation of viable and nonviable tissues has occurred.
3. When source control in a severely septic patient is required, the effective intervention associated with the least physiologic insult should be used (e.g., percutaneous rather than surgical drainage of an abscess).
4. If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly after other vascular access has been established.

INFECTION PREVENTION

1a. Selective oral decontamination and selective digestive decontamination should be introduced and investigated as a method to reduce the incidence of ventilator-associated pneumonia; this infection control measure can then be instituted in healthcare settings and regions where this methodology is found to be effective.
1b. Oral chlorhexidine gluconate be used as a form of oropharyngeal decontamination to reduce the risk of ventilator-associated pneumonia in ICU patients with severe sepsis.

Surviving Sepsis Campaign Care Bundles

To be completed within 3 hr:
1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad-spectrum antibiotics
4. Administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L

To be completed within 6 hr:
5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65 mm Hg
6. In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (≥36 mg/dL)
7. Measure central venous pressure (CVP)*
8. Measure central venous oxygen saturation (ScvO₂)*
9. Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, ScvO₂ of ≥70%, and normalization of lactate.


Table 70-11

Recommendations: Hemodynamic Support and Adjunctive Therapy—Adults

**FLUID THERAPY OF SEVERE SEPSIS**
1. Crystalloids as the initial fluid of choice in the resuscitation of severe sepsis and septic shock.
2. Against the use of hydroxethyl starches for fluid resuscitation of severe sepsis and septic shock.
3. Albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids.
4. Initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemia to achieve a minimum of 30 mL/kg of crystalloids (a portion of this may be albumin equivalent). More rapid administration and greater amounts of fluid may be needed in some patients.
5. Fluid challenge technique be applied wherein fluid administration is continued as long as there is hemodynamic improvement either based on dynamic (e.g., change in pulse pressure, stroke volume variation) or static (e.g., arterial pressure, heart rate) variables.

**VASOPRESSORS**
1. Vasopressor therapy initially to target a mean arterial pressure (MAP) of 65 mm Hg.
2. Norepinephrine as the first choice vasopressor.
3. Epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure.
4. Vasopressin 0.03 units/min can be added to norepinephrine (NE) with intent of either raising MAP or decreasing NE dosage.
5. Low-dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension and vasopressin doses higher than 0.03-0.04 units/min should be reserved for salvage therapy (failure to achieve adequate MAP with other vasopressor agents).
6. Dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (e.g., patients with low risk of tachyarrhythmias and absolute or relative bradycardia).
7. Phenylephrine is not recommended in the treatment of septic shock except in circumstances where (a) NE is associated with serious arrhythmias, (b) cardiac output is known to be high and blood pressure persistently low, or (c) as salvage therapy when combined inotrope/vasopressor drugs and low-dose vasopressin have failed to achieve MAP target.
8. Low-dose dopamine should not be used for renal protection.
9. All patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available.

**INOTROPIC THERAPY**
1. A trial of dobutamine infusion up to 20 µg/kg/min be administered or added to vasopressor (if in use) in the presence of (a) myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output, or (b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP.
2. Not using a strategy to increase cardiac index to predetermined supranormal levels.

**CORTICOSTEROIDS**
1. Not using intravenous hydrocortisone to treat adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability (see goals for Initial Resuscitation). In case this is not achievable, we suggest intravenous hydrocortisone alone at a dose of 200 mg per day.
2. Not using the ACTH stimulation test to identify adults with septic shock who should receive hydrocortisone.
3. In treated patients, hydrocortisone tapered when vasopressors are no longer required.
4. Corticosteroids should not be administered for the treatment of sepsis in the absence of shock.
5. When hydrocortisone is given, use continuous flow.

Table 70-12  Recommendations: Special Considerations in Pediatrics

### INITIAL RESUSCITATION
1. For respiratory distress and hypoxemia start with face mask oxygen or if needed and available, high flow nasal cannula oxygen or nasopharyngeal CPAP (NP CPAP). For improved circulation, peripheral intravenous access or intraosseous access can be used for fluid resuscitation and intrope infusion when a central line is not available. If mechanical ventilation is required then cardiovascular instability during intubation is less likely after appropriate cardiovascular resuscitation.
2. Initial therapeutic end points of resuscitation of septic shock: capillary refill of ≤2 sec, normal blood pressure for age, normal pulses with no differential between peripheral and central pulses, warm extremities, urine output >1 mL kg⁻¹ hr⁻¹, and normal mental status. ScvO₂ saturation ≥70% and cardiac index between 3.3 and 6.0 L/min/m² should be targeted thereafter.
3. Follow American College of Critical Care Medicine-Pediatric Life Support (ACCM-PALS) guidelines for the management of septic shock.
4. Evaluate for and reverse pneumothorax, pericardial tamponade, or endocrine emergencies in patients with refractory shock.

### ANTIBIOTICS AND SOURCE CONTROL
1. Empiric antibiotics should be administered within 1 hr of the identification of severe sepsis. Blood cultures should be obtained before administering antibiotics when possible but this should not delay administration of antibiotics. The empiric drug choice should be changed as epidemic and endemic ecologies dictate (e.g., H1N1, methicillin-resistant Staphylococcus aureus [MRSA], chloroquine-resistant malaria, penicillin-resistant pneumococci, recent ICU stay, neutropenia).
2. Clindamycin and antitoxin therapies for toxic shock syndromes with refractory hypotension.
3. Early and aggressive source control.
4. Clostridium difficile colitis should be treated with enteral antibiotics if tolerated. Oral vancomycin is preferred for severe disease.

### FLUID RESUSCITATION
1. In the industrialized world with access to inotropes and mechanical ventilation, initial resuscitation of hypovolemic shock begins with infusion of isotonic crystallloids or albumin with boluses of up to 20 mL/kg crystallloids (or albumin equivalent) over 5-10 minutes, titrated to reversing hypotension, increasing urine output, and attaining normal capillary refill, peripheral pulses, and level of consciousness without inducing hepatomegaly or rales. If hepatomegaly or rales exist then inotropic support should be implemented, not fluid resuscitation. In nonhypotensive children with severe hemolytic anemia (severe malaria or sickle cell crises), blood transfusion is considered superior to crystallloid or albumin bolus.

### INOTROPES/VASOPRESSORS/VASODILATORS
1. Begin peripheral inotropic support until central venous access can be attained in children who are not responsive to fluid resuscitation.
2. Patients with low cardiac output and elevated systemic vascular resistance states with normal blood pressure should be given vasodilator therapies in addition to inotropes.

### EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO)
1. Consider ECMO for refractory pediatric septic shock and respiratory failure.

### CORTICOSTEROIDS
1. Timely hydrocortisone therapy in children with fluid refractory, catecholamine resistant shock and suspected or proven absolute (classic) adrenal insufficiency.

### PROTEIN C AND ACTIVATED PROTEIN CONCENTRATE
No recommendation as no longer available.

### BLOOD PRODUCTS AND PLasma THERAPIES
1. Similar hemoglobin targets in children as in adults. During resuscitation of low superior vena cava oxygen saturation shock (<70 %), hemoglobin levels of 10 g/dL are targeted. After stabilization and recovery from shock and hypoxemia, a lower target (>7.0 g/dL) can be considered reasonable.
2. Similar platelet transfusion targets in children as in adults.
3. Use plasma therapies in children to correct sepsis-induced thrombotic purpura disorders, including progressive disseminated intravascular coagulation, secondary thrombotic microangiopathy, and thrombotic thrombocytopenic purpura.

### MECHANICAL VENTILATION
1. Lung-protective strategies during mechanical ventilation.

### SEDATION/ANALGESIA/DRUG TOXICITIES
1. We recommend use of sedation with a sedation goal in critically ill mechanically ventilated patients with sepsis.
2. Monitor drug toxicity labs because drug metabolism is reduced during severe sepsis, putting children at greater risk of adverse drug-related events.

### GLYCEMIC CONTROL
1. Control hyperglycemia using a similar target as in adults (≤180 mg/dL). Glucose infusion should accompany insulin therapy in newborns and children because some hyperglycemic children make no insulin whereas others are insulin resistant.

### DIURETICS AND RENAL REPLACEMENT THERAPY
1. Use diuretics to reverse fluid overload when shock has resolved, and if unsuccessful then continuous venovenous hemofiltration (CVVH) or intermittent dialysis to prevent >10% total body weight fluid overload.

### DEEP VEIN THROMBOSIS (DVT) PROPHYLAXIS
No recommendation on the use of DVT prophylaxis in prepubertal children with severe sepsis.

### STRESS ULCER (SU) PROPHYLAXIS
No recommendation on the use of SU prophylaxis in prepubertal children with severe sepsis.

### NUTRITION
1. Enteral nutrition given to children who can be fed enterally, and parenteral feeding in those who cannot (grade 2C).

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*CPAP, continuous positive airway pressure.

plus cefotaxime and/or gentamicin. Acyclovir should be added if herpes simplex virus is suspected clinically. In infants and children, community-acquired infections with Neisseria meningitidis can initially be treated empirically with a 3rd-generation cephalosporin (ceftriaxone or cefotaxime). Haemophilus influenzae infections can be treated empirically with a 3rd-generation cephalosporin (ceftriaxone or cefotaxime). The prevalence of resistant Streptococcus pneumoniae requires the addition of vancomycin. Suspicion of community- or hospital-acquired, methicillin-resistant Staphylococcus aureus infection warrants coverage with vancomycin, depending on local resistance patterns. If an intraabdominal process is suspected, anaerobic coverage should be included with an agent such as metronidazole, clindamycin, or piperacillin-tazobactam.

Nosocomial sepsis should generally be treated with at least a 3rd- or 4th-generation cephalosporin or a penicillin with an extended Gram-negative spectrum (e.g., piperacillin-tazobactam). An aminoglycoside should be added as the clinical situation warrants. Vancomycin should be added to the regimen if the patient has an indwelling medical device (see Chapter 179), Gram-positive cocci are isolated from the blood, methicillin-resistant S. aureus infection is suspected, or as empiric coverage for S. pneumoniae in a patient with meningitis. Empirical coverage for fungal infections should be considered for selected immuno compromised patients (see Chapter 178). It should be noted that these are broad, generalized recommendations that must be tailored to the individual clinical scenario and to the local resistance patterns of the community and/or hospital.

Distributive shock that is not secondary to sepsis is caused by a primary abnormality in vascular tone. Cardiac output in affected patients is usually maintained and may initially be supranormal. These patients may benefit temporarily from volume resuscitation, but the early initiation of a vasoconstrictive agent to increase SVR is important element of clinical care. Patients with spinal cord injury and spinal shock may benefit from either phenylephrine or vasopressin to increase SVR, and epinephrine is the treatment of choice for patients with anaphylaxis (Table 70-13). Epinephrine has peripheral α-adrenergic as well as inotropic effects that may improve the myocardial depression seen with anaphylaxis and its associated inflammatory response (see Chapter 149).

Patients with cardiogenic shock have poor cardiac output secondary to systolic and/or diastolic myocardial depression, often with a compensatory elevation in SVR. These patients may show poor response to fluid resuscitation and may decompensate quickly when fluids are administered. Smaller boluses of fluid (5-10 mL/kg) should be given in cardiogenic shock to replace deficits and maintain preload. In any patient with shock whose clinical status deteriorates with fluid resuscitation, a cardiogenic etiology should be considered, and further administration of intravenous fluids should be provided judiciously. Early initiation of myocardial support with epinephrine or dopamine to improve cardiac output is important in this context and early consideration should be given to administration of inodilator, such as milrinone.

Despite adequate cardiac output with the support of inotropic agents, a high SVR with poor peripheral perfusion and acidosis may persist in cardiogenic shock. Therefore, if not already started, milrinone therapy may improve systolic function and decrease SVR without causing a significant increase in heart rate. Furthermore, this agent has the added benefit of enhancing diastolic relaxation. Dobutamine or other vasodilating agents, such as nitroprusside, may also be considered in this setting (Table 70-14). Titration of these agents should target clinical end points, including increased urine output, improved peripheral perfusion, resolution of acidosis, and normalization of mental status. Even though they may be beneficial in other forms of shock, agents that improve blood pressure by increasing SVR, such as norepinephrine and vasopressin, should generally be avoided in patients with cardiogenic shock. These agents may cause further decomposition and potentially precipitate cardiac arrest as a result of the increased afterload and additional work imposed on the myocardium. The combination of inotropic and vasoactive agents must be tailored to the pathophysiology of the individual patient with close and frequent reassessment of the patient’s cardiovascular status.

For patients with obstructive shock, fluid resuscitation may be briefly temporizing in maintaining cardiac output, but the primary insult must be immediately addressed. Examples of lifesaving therapeutic interventions for such patients are pericardiocentesis for pericardial effusion, pleurocentesis or chest tube placement for pneumothorax, thrombectomy/thrombolysis for pulmonary embolism, and the initiation of a prostaglandin infusion for ductus-dependent cardiac lesions. There is often a “last-drop” phenomenon associated with some obstrusive lesions, in that small additional amounts of intravascular volume depletion may lead to a rapid deterioration, including cardiac arrest, if the obstructive lesion is not corrected.

Regardless of the etiology of shock, metabolic status should be meticulously maintained (see Table 70-8). Electrolyte levels should be monitored closely and corrected as needed. Hypoglycemia is common and should be promptly treated. Neonates and infants in particular may have profound glucose dysregulation in association with shock. Glucose levels should be checked routinely and treated appropriately, especially early in the course of illness. Hypocalcemia, which may contribute to myocardial dysfunction, should be treated with a goal of normalizing the ionized calcium concentration. There is no evidence that supranormal calcium levels benefit the myocardium, and hypercalcemia may actually be associated with increased myocardial toxicity.

Adrenal function is another important consideration in shock, and hydrocortisone replacement may be beneficial. Up to 50% of critically ill patients may have absolute or relative adrenal insufficiency. Patients at risk for adrenal insufficiency include those with congenital adrenal hypoplasia, abnormalities of the hypothalamic-pituitary axis, and

| Table 70-13 Cardiovascular Drug Treatment of Shock |
|----------------|----------------|----------------|
| **DRUG**      | **EFFECT(S)**                          | **DOsing RANGE** |
| Dopamine      | ↑ Cardiac contractility                  | 3-20 µg/kg/min  |
|               | Significant peripheral vasoconstriction  |                  |
|               | at >10 µg/kg/min                         |                  |
| Epinephrine   | ↑ Heart rate and ↑ cardiac contractility | 0.05-3.0 µg/kg/min |
|               | Potent vasoconstrictor                   |                  |
| Dobutamine    | ↑ Cardiac contractility                  | 1-10 µg/kg/min   |
|               | Peripheral vasodilator                   |                  |
| Norepinephrine| Potent vasoconstriction                  | 0.05-1.5 µg/kg/min|
|               | No significant effect on cardiac contractility |                  |
| Phenylephrine | Potent vasoconstriction                  | 0.5-2.0 µg/kg/min|
|               | Can cause sudden hypertension            |                  |
|               | ↑ O2 consumption                         |                  |
Table 70-14  | Vasodilators/Afterload Reducers

<table>
<thead>
<tr>
<th>DRUG</th>
<th>EFFECT(S)</th>
<th>DOSSING RANGE</th>
<th>COMMENT(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroprusside</td>
<td>Vasodilator (mainly arterial)</td>
<td>0.5-4.0 µg/kg/min</td>
<td>Rapid effect&lt;br&gt;Risk of cyanide toxicity with prolonged use (&gt;96 hr)</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Vasodilator (mainly venous)</td>
<td>1-20 µg/kg/min</td>
<td>Rapid effect&lt;br&gt;Risk of increased intracranial pressure</td>
</tr>
<tr>
<td>Prostaglandin E₁</td>
<td>Maintains an open ductus arteriosus in the newborn with ductal-dependent congenital heart disease</td>
<td>0.01-0.2 µg/kg/min</td>
<td>Can lead to hypotension&lt;br&gt;Risk of apnea</td>
</tr>
<tr>
<td>Milrinone</td>
<td>Increased cardiac contractility</td>
<td>Load 50 µg/kg over 15 min</td>
<td>Phosphodiesterase inhibitor—slows cyclic adenosine monophosphate breakdown</td>
</tr>
</tbody>
</table>

Recent therapy with corticosteroids (including patients with asthma, rheumatic diseases, malignancies, and inflammatory bowel disease). These patients are at high risk for adrenal dysfunction and should receive stress doses of hydrocortisone. Steroids may also be considered in patients with shock that is unresponsive to fluid resuscitation and catecholamines. While there may be a subset of pediatric septic shock patients that benefit from treatment with hydrocortisone, currently available pediatric data do not demonstrate an overall survival benefit in patients with shock treated with hydrocortisone. Determination of baseline cortisol levels prior to steroid administration may be beneficial in guiding therapy, although this idea remains controversial.

**Considerations for Continued Therapy**

After the 1st hr of therapy and attempts at early reversal of shock, focus on goal-directed endpoints should continue in an intensive care setting (see Fig. 70-1 and Table 70-8). Clinical endpoints serve as global markers for organ perfusion and oxygenation. Laboratory parameters such as SVO₂ (or ScvO₂), serum lactate concentration, cardiac index, and hemoglobin serve as adjunctive measures of tissue oxygen delivery. Hemoglobin should be maintained at 10 g/dL, SVO₂ (or ScvO₂) >70%, and cardiac index at 3.3-6.0 L/min/m² to optimize oxygen delivery in the acute phase of shock. It is important to note that cardiac index is rarely monitored in the clinical setting owing to the limited use of pulmonary artery catheters and the lack of accurate noninvasive cardiac output monitors for infants and children. Blood lactate levels and calculation of base deficit from arterial blood gas values are very useful markers for the adequacy of oxygen delivery. These traditional markers are all indicators of global oxygen utilization and delivery, and there is increasing interest in measures of local tissue oxygenation including near infra-red spectroscopy of the cerebrum, flank, or abdomen.

Respiratory support should be used as clinically appropriate. When shock leads to ARDS requiring mechanical ventilation, lung-protective strategies to keep plateau pressure below 30 cm H₂O and maintain tidal volume at 6 mL/kg have been shown to improve mortality in adult patients (see Chapter 71). These data are extrapolated to pediatric patients because of the lack of definitive pediatric studies in this area. Additionally, after the initial shock state has been reversed, data demonstrate that judicious fluid administration, renal replacement therapy, and fluid removal may also be useful in children with anuria or oliguria and fluid overload (see Chapter 535). Other interventions include correction of coagulopathy with fresh frozen plasma or cryoprecipitate and platelet transfusions as necessary, especially in the presence of active bleeding.

If shock remains refractory despite maximal therapeutic interventions, mechanical support with **extracorporeal membrane oxygenation** or a **ventricular assist device** may be indicated. Extracorporeal membrane oxygenation may be lifesaving in cases of refractory shock regardless of underlying etiology. Similarly, a ventricular assist device may be indicated for refractory cardiogenic shock in the setting of cardiomyopathy or recent cardiac surgery. Systemic anticoagulation, which is required while patients are receiving mechanical support, may be difficult, given the significant coagulopathy often encountered in refractory shock, especially when the underlying etiology is sepsis. Mechanical support in refractory shock poses substantial risks but can improve survival in specific populations of patients.

**PROGNOSIS**

In septic shock, mortality rates are as low as 3% in previously healthy children and 6-9% in children with chronic illness (compared with 25-30% in adults). With early recognition and therapy, the mortality rate for pediatric shock continues to improve, but shock and MODS remain one of the leading causes of death in infants and children. The risk of death involves a complex interaction of factors, including the underlying etiology, presence of chronic illness, host immune response, and timing of recognition and therapy.

Bibliography is available at Expert Consult.
Bibliography


The term respiratory distress is often used to indicate signs and symptoms of abnormal respiratory pattern. A child with nasal flaring, tachypnea, chest wall retractions, stridor, grunting, dyspnea, and wheezing is often judged as having respiratory distress. The magnitude of these findings is used to judge the clinical severity of respiratory distress. Although nasal flaring is a nonspecific sign, the other signs are useful in localizing the site of pathology (see Chapters 373 and 374). Respiratory failure is defined as inability of the lungs to provide sufficient oxygen (hypoxic respiratory failure) or remove carbon dioxide (ventilatory failure) to meet metabolic demands. Whereas respiratory
distress is a clinical impression, the diagnosis of respiratory failure indicates inadequacy of oxygenation or ventilation, or both. Respiratory distress can occur in patients without respiratory disease, and respiratory failure can occur in patients without respiratory distress.

**RESPIRATORY DISTRESS**

A careful physical examination must be performed when managing a child in respiratory distress. Nasal flaring is an extremely important sign of distress, especially in infants. It is indicative of discomfort, pain, fatigue, or breathing difficulty. The state of responsiveness is another crucial sign. Lethargy, disinterest in surroundings, and poor cry are suggestive of exhaustion, hypercarbia, and impending respiratory failure. Abnormalities of the rate and depth of respirations can occur with both pulmonary and nonpulmonary causes of respiratory distress. In diseases of decreased lung compliance, such as pneumonia and pulmonary edema, respirations are characteristically rapid and shallow (decreased tidal volume). In obstructive airway diseases, such as asthma and laryngotracheitis, respirations are deep (increased tidal volume) but less rapid. Rapid and deep respirations without other respiratory signs should alert the physician to the possibility of non-respiratory causes of respiratory distress, such as response to metabolic acidosis (diabetic ketoacidosis, renal tubular acidosis) or stimulation of the respiratory center (encephalitis, ingestion of central nervous system [CNS] stimulants). Chest wall, suprasternal, and subcostal retractions are manifestations of increased inspiratory effort, weak chest wall, or both. Inspiratory stridor indicates airway obstruction above the thoracic inlet, whereas expiratory wheezing results from airway obstruction below the thoracic inlet. Grunting is most commonly heard in diseases with decreased functional residual capacity (e.g., pneumonia, pulmonary edema) and peripheral airway obstruction (e.g., bronchiolitis).

**Respiratory Disease Manifesting as Respiratory Distress**

Clinical examination is important in localizing the site of pathology (see Chapter 373). Extrathoracic airway obstruction occurs anywhere above the thoracic inlet. Inspiratory stridor, suprasternal, chest wall, and subcostal retractions, and prolongation of inspiration are hallmarks of extrathoracic airway obstruction. By comparison, features of intrathoracic airway obstruction are prolongation of expiration and expiratory wheezing. Typical manifestations of alveolar interstitial pathology are rapid, shallow respirations, chest wall retractions, and grunting. The site of pathology can be localized and the differential diagnosis established on the basis of the clinical signs and symptoms (Tables 71-1 and 71-2).

**Respiratory Distress without Respiratory Disease**

Although respiratory distress most commonly results from diseases of lungs, airways, and chest wall, pathology in other organ systems can manifest as “respiratory distress” and lead to misdiagnosis and inappropriate management (Table 71-3). Respiratory distress resulting from heart failure or diabetic ketoacidosis may be misdiagnosed as asthma and improperly treated with albuterol, resulting in worsened hemodynamic state or ketoacidosis. Careful history and physical examination provide essential clues in avoiding misdiagnosis.

<table>
<thead>
<tr>
<th><strong>SITE OF PATHOLOGY</strong></th>
<th><strong>RESPIRATORY RATE</strong></th>
<th><strong>RETRACTIONS</strong></th>
<th><strong>AUDIBLE SOUNDS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrathoracic airway</td>
<td>↑</td>
<td>↑↑↑↑↑</td>
<td>Stridor</td>
</tr>
<tr>
<td>Intrathoracic extrapulmonary</td>
<td>↑</td>
<td>↑↑</td>
<td>Wheezing</td>
</tr>
<tr>
<td>Intrathoracic intrapulmonary</td>
<td>↑↑</td>
<td>↑↑</td>
<td>Wheezing</td>
</tr>
<tr>
<td>Alveolar interstitial</td>
<td>↑↑↑↑↑</td>
<td>↑↑↑↑</td>
<td>Grunting</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>RESPIRATORY DISTRESS</strong></th>
<th><strong>CENTRAL AIRWAY OBSTRUCTION</strong></th>
<th><strong>THORACIC CAGE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Choanal atresia</td>
<td>Retropharyngeal/peritonsillar abscess</td>
<td>Kypsoaclosis</td>
</tr>
<tr>
<td>Tonsilloadenoidal hypertrophy</td>
<td>Laryngomalacia</td>
<td>Diaphragmatic hernia</td>
</tr>
<tr>
<td>Adenoidal hypertrophy</td>
<td>Epiglottitis</td>
<td>Flail chest</td>
</tr>
<tr>
<td>Congenital stenosis</td>
<td>Vocal cord paralysis</td>
<td>Eversion of diaphragm</td>
</tr>
<tr>
<td>Tracheal stenosis</td>
<td>Laryngotracheitis</td>
<td>Asphyxiating thoracic dystrophy</td>
</tr>
<tr>
<td>Tracheal stenosis</td>
<td>Subglottic stenosis</td>
<td>Prune-belly syndrome</td>
</tr>
<tr>
<td>Tracheal stenosis</td>
<td>Vascular ring/pulmonary sling</td>
<td>Dermatomyositis</td>
</tr>
<tr>
<td>Tracheal stenosis</td>
<td>Mediastinal mass</td>
<td>Abdominal distention</td>
</tr>
<tr>
<td>Tracheal stenosis</td>
<td>Foreign-body aspiration</td>
<td></td>
</tr>
<tr>
<td>Tracheal stenosis</td>
<td>Obstructive sleep apnea</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>ALVEOLAR-INTERSTITIAL DISEASE</strong></th>
<th><strong>RESPIRATORY PUMP</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobar pneumonia</td>
<td>CENTRAL AIRWAY OBSTRUCTION</td>
</tr>
<tr>
<td>Acute respiratory distress</td>
<td>THORACIC CAGE</td>
</tr>
</tbody>
</table>
| syndrome/hyaline membrane disease | ]
| Interstitial pneumonia            | BRAINSTEM |
| Hydrocarbon pneumonia             | Arnold-Chiari malformation |
| Pulmonary hemorrhage/hemosiderosis| Central hypoventilation syndrome |

<table>
<thead>
<tr>
<th><strong>PERIPHERAL AIRWAY OBSTRUCTION</strong></th>
<th><strong>RESPIRATORY PUMP</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>LUNG</td>
</tr>
<tr>
<td>Bronchiolitis</td>
<td>CENTRAL AIRWAY OBSTRUCTION</td>
</tr>
<tr>
<td>Foreign-body aspiration</td>
<td>THORACIC CAGE</td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
<td>Kypsoaclosis</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Diaphragmatic hernia</td>
</tr>
<tr>
<td>α1-Antitrypsin deficiency</td>
<td>Flail chest</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>SPINAL CORD DISEASE</strong></th>
<th><strong>RESPIRATORY PUMP</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma</td>
<td>LUNG</td>
</tr>
<tr>
<td>Transverse myelitis</td>
<td>CENTRAL AIRWAY OBSTRUCTION</td>
</tr>
<tr>
<td>Spinal muscular atrophy</td>
<td>THORACIC CAGE</td>
</tr>
<tr>
<td>Poliomyelitis</td>
<td>Kypsoaclosis</td>
</tr>
<tr>
<td>Tumor/abscess</td>
<td>Diaphragmatic hernia</td>
</tr>
</tbody>
</table>

**Cardiovascular Disease Manifesting as Respiratory Distress**

A child with cardiovascular pathology may present with respiratory distress caused by 2 mechanisms: (1) decreased lung compliance and (2) cardiogenic shock (Table 71-4). Diseases that result in an increased pulmonary arterial blood flow (e.g., left-to-right shunts) or increased pulmonary venous pressure (e.g., left ventricular dysfunction from hypertension or myocarditis, obstructed total anomalous pulmonary...
venous return) cause an increase in pulmonary capillary pressure and transudation of fluid into the pulmonary interstitium and alveoli. The increased pulmonary blood and water content leads to decreased lung compliance and results in rapid shallow respirations.

It is important to recognize that interstitial lung edema can not only manifest as alveolar fluid, but as small airway obstruction as well. Wheezing as a sign of congestive cardiac disease is common in infants and young children and should be recognized. Patients with cardiac lesions that result in a low cardiac output state, such as obstructive lesions of left side of the heart and acquired or congenital cardiomyopathy, often present in a state of shock with decreased tissue perfusion and metabolic acidosis. Such children demonstrate respiratory distress because of stimulation of chemoreceptors by metabolic acidosis and stimulation of baroreceptors by decreased blood pressure. The likelihood of a particular cardiovascular illness manifesting as respiratory distress depends on age at presentation (Table 71-5).

### Neurologic Disease Manifesting as Respiratory Distress

CNS dysfunction can lead to alterations in respiratory patterns. Increased intracranial pressure (ICP) may manifest as respiratory distress. Early rise in ICP results in stimulation of respiratory centers, leading to increases in the rate (tachypnea) and depth (hyperpnea) of respiration. The resultant decrease in PaCO2 and elevation of cerebrospinal fluid pH lead to cerebral vasoconstriction and amelioration of intracranial hypertension. Cerebral hemispheric and midbrain lesions often result in hyperpnea as well as tachypnea. In such situations, blood gas measurements typically show respiratory alkalosis without hypoxemia. Pathology affecting the pons and medulla manifests as irregular breathing patterns such as apneustic breathing (prolonged inspiration), Cheyne-Stokes breathing (alternate periods of rapid and slow breathing), and irregular, ineffective breathing or apnea. Level of consciousness is most often impaired when abnormal breathing pattern from a brainstem disorder is present. Along with respiratory changes, other manifestations of CNS dysfunction and increased ICP may be present, such as focal neurologic signs, pupillary changes, hypertension, and bradycardia (see Chapter 63). Occasionally, severe CNS dysfunction can result in neurogenic pulmonary edema and respiratory distress, which may be a result of excessive sympathetic discharge resulting in increased pulmonary venous hydrostatic pressure as well as increased pulmonary capillary pressure.

### Table 71-4 Cardiovascular Pathology Manifesting as Respiratory Distress

<table>
<thead>
<tr>
<th>AGE</th>
<th>MECHANISM</th>
<th>DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn (1-10 days)</td>
<td>Arteriovenous pressure difference</td>
<td>Pulmonary venous return (PVR)</td>
</tr>
<tr>
<td>Young Infant (1-6 mo)</td>
<td>Pulmonary vascular resistance</td>
<td>Left-to-right shunt</td>
</tr>
<tr>
<td>Any Age</td>
<td>Rate disturbance</td>
<td>Tachy- or bradyarrhythmias</td>
</tr>
</tbody>
</table>

### Table 71-5 Typical Chronology of Heart Disease Presentation in Children

<table>
<thead>
<tr>
<th>AGE</th>
<th>MECHANISM</th>
<th>DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn (1-10 days)</td>
<td>Arteriovenous pressure difference</td>
<td>Pulmonary venous obstruction</td>
</tr>
<tr>
<td>Young Infant (1-6 mo)</td>
<td>Pulmonary vascular resistance</td>
<td>Transposition of the great arteries</td>
</tr>
</tbody>
</table>

---

### Table 71-3 Nonpulmonary Causes of Respiratory Distress

<table>
<thead>
<tr>
<th>EXAMPLE(S)</th>
<th>MECHANISM(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Pulmonary blood/water content, Metabolic acidosis, Baroreceptor stimulation</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Stimulation of brainstem respiratory centers, Stimulation of peripheral chemoreceptors</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Cytokine stimulation of respiratory centers, Baroreceptor stimulation from shock, Metabolic acidosis</td>
</tr>
</tbody>
</table>

### Table 71-4 Cardiovascular Pathology Manifesting as Respiratory Distress

I. DECREASED LUNG COMPLIANCE
   A. Left-to-Right Shunts
      1. Ventricular septal defect, atrial septal defect, patent ductus arteriosus, atrioventricular canal, truncus arteriosus
      2. Cerebral or hepatic arteriovenous fistula
   B. Ventricular Failure
      1. Left-heart obstructive lesions
         a) aortic stenosis
         b) coarctation of the aorta
         c) mitral stenosis
         d) interrupted aortic arch
         e) hypoplastic left heart syndrome
      2. Myocardial infarction
         a) anomalous left coronary artery arising from the pulmonary artery
      3. Hypertension
         a) acute glomerulonephritis
      4. Inflammatory/infectious
         a) myocarditis
         b) pericardial effusion
      5. Idiopathic
         a) dilated cardiomyopathy
         b) hypertrophic obstructive cardiomyopathy
   C. Pulmonary Venous Obstruction
      1. Total anomalous pulmonary venous return with obstruction
      2. Cor triatriatum

II. SHOCK RESULTING IN METABOLIC ACIDOSIS
   A. Left-Heart Obstructive Lesions
   B. Acute Ventricular Failure
      1. Myocarditis, myocardial infarction

permeability. Central neurogenic hyperventilation is characteristically observed in CNS involvement by illnesses such as urea cycle defects and encephalitis. Bradycardia and apnea may be caused by CNS-depressant medications, poisoning, prolonged hypoxia, trauma, or infection (see Table 71-2).

**Toxic-Metabolic States Manifesting as Respiratory Distress**

Direct stimulation of respiratory centers resulting in respiratory alkalosis is encountered in certain intoxications, such as those involving salicylates and theophylline. Similarly, intoxication with general CNS stimulants, such as cocaine and amphetamines may manifest as increased respirations. Presence of endogenous and exogenous CNS stimulants, such as organic acidemias, ingestion of methanol and ethylene glycol, and late stages of salicylism, cause metabolic acidosis and compensatory hyperventilation, which can manifest as respiratory distress. Blood gas measurements show decreased pH and compensatory hypocarbia with normal oxygenation. Metabolic disorders causing hyperammonemia, on the other hand, cause respiratory alkalosis (decreased PaCO₂ with increased pH) because ammonia is a stimulant of respiratory centers.

**Other Nonpulmonary Entities Manifesting as Respiratory Distress**

Sepsis and septic shock may manifest as respiratory distress by causing acute respiratory distress syndrome (ARDS), hypovolemic stimulation of baroreceptors, stimulation of respiratory centers by cytokines, and lactic acidosis. Other indirect causes of lung injury include systemic inflammatory conditions, trauma, transfusion-related acute lung injury, and pancreatitis. Similarly, renal disease may manifest as respiratory distress by causing metabolic acidosis (e.g., renal tubular acidosis or renal failure) or hypertensive left ventricular failure and fluid overload.

### RESPIRATORY FAILURE

Respiratory failure occurs when oxygenation and ventilation are insufficient to meet the metabolic demands of the body. Respiratory failure may result from an abnormality in (1) lung and airways, (2) chest wall and muscles of respiration, or (3) central and peripheral chemoreceptors. Clinical manifestations depend largely on the site of pathology (Table 71-6). Although respiratory failure is traditionally defined as respiratory dysfunction resulting in PaO₂ <60 mm Hg with breathing of room air and PaCO₂ >50 torr resulting in acidosis, the patient's general state, respiratory effort, and potential for impending exhaustion are more important indicators than blood gas values.

Acute lung injury due to pneumonia, sepsis, aspiration, drowning, embolism, trauma, smoke inhalation, or drug overdose may lead to the ARDS (Tables 71-7 and 71-8; Fig. 71-1).

### Pathophysiology of Respiratory Failure

Respiratory failure can be classified into (1) hypoxic respiratory failure (failure of oxygenation) and (2) hypercarbic respiratory failure (failure of ventilation). Systemic venous (pulmonary arterial) blood is arterialized after equilibration with alveolar gas in the pulmonary capillaries and is carried back to the heart by pulmonary veins. The arterial gas is influenced by the composition of inspired gas, and the effectiveness of alveolar ventilation, pulmonary capillary perfusion, and diffusion capacity of the alveolar capillary membrane. Abnormality at any of these steps can result in respiratory failure. Hypoxic respiratory failure results from intrapulmonary shunting and venous admixture or insufficient diffusion of oxygen from alveoli into pulmonary capillaries. This can be

---

**Table 71-6** Typical Clinical Manifestations of Respiratory Failure

<table>
<thead>
<tr>
<th>SITE OF PATHOLOGY</th>
<th>SYMPTOM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung and Airways</td>
<td>Nasal flaring, retractions, tachypnea, wheezing, stridor, grunting</td>
</tr>
<tr>
<td>Chest wall and muscles of respiration</td>
<td>Nasal flaring, tachypnea, paradoxical respirations</td>
</tr>
<tr>
<td>Respiratory control</td>
<td>Shallow or slow respirations, abnormal respiratory patterns, apnea</td>
</tr>
</tbody>
</table>

**Table 71-7** Simplified Consensus Definition of Acute Lung Injury

- Acute onset (<7 days)
- Severe hypoxemia (PaO₂/FIO₂ <300 for acute lung injury, or <200 for acute respiratory distress syndrome)
- Diffuse bilateral pulmonary infiltrates on frontal radiograph consistent with pulmonary edema (these can be patchy and asymmetric, and pleural effusions can be present)
- Absence of left atrial hypertension (pulmonary artery wedge pressure <18 mm Hg if measured)


---

**Table 71-8** New Berlin Definition of ARDS in Infancy and Early Childhood

<table>
<thead>
<tr>
<th>BERLIN DEFINITION CRITERIA</th>
<th>SUITABILITY IN INFANTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timing</strong></td>
<td>Within 1 wk of a known clinical insult or new or worsening respiratory symptoms</td>
</tr>
<tr>
<td>Chest X-rays or tomography scan</td>
<td>Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules. (Illustrative clinical cases and chest X-rays have been provided)</td>
</tr>
<tr>
<td>Origin of edema</td>
<td>Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema, if no ARDS risk factors are present</td>
</tr>
<tr>
<td>Oxygenation*</td>
<td>200 mm Hg &lt; PaO₂/FIO₂ ≤ 300 mm Hg with PEEP or CPAP ≥ 5 cm H₂O, 100 mm Hg &lt; PaO₂/FIO₂ ≤ 200 mm Hg with PEEP ≥ 5 cm H₂O, PaO₂/FIO₂ &lt; 100 mm Hg with PEEP ≥ 5 cm H₂O</td>
</tr>
</tbody>
</table>

**New Berlin Definition of ARDS in Infancy and Early Childhood**

*If altitude is higher than 1,000 m, the correction factor should be calculated as follows: [PaO₂/FIO₂ × (barometric pressure/760)].

†This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

CPAP, continuous positive airway pressure; FIO₂, fraction of inspired oxygen; PaO₂, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.
caused by conditions such as small airway obstruction, increased barrier to diffusion (such as interstitial edema or fibrosis), or in conditions where alveoli are collapsed or filled with fluid (e.g., ARDS, pneumonia, atelectasis, or pulmonary edema). In most cases, hypoxic respiratory failure is associated with a decreased functional residual capacity, and can be managed by recruitment with positive pressure ventilation. Hypercarbic respiratory failure is caused by decreased minute alveolar ventilation (tidal volume multiplied by respiratory rate). This can occur from centrally-mediated disorders of respiratory drive, increased dead space ventilation, or obstructive airway disease. The two entities may coexist as a combined failure of oxygenation and ventilation.

**Ventilation–Perfusion Mismatch, Venous Admixture, Intrapulmonary Shunt**

For exchange of O\(_2\) and CO\(_2\) to occur, alveolar gas must be exposed to blood in pulmonary capillaries. Both ventilation and perfusion are lower in nondependent areas of the lung and higher in dependent areas of the lung. The difference in perfusion (Q) is greater than the difference in ventilation (V). Perfusion in excess of ventilation results in incomplete “arterialization” of systemic venous (pulmonary arterial) blood and is referred to as venous admixture. Perfusion of unventilated areas is referred to as intrapulmonary shunting of systemic venous blood to systemic arterial circulation. Conversely, ventilation that is in excess of perfusion is “wasted”; that is, it does not contribute to gas exchange and is referred to as dead space ventilation. Dead space ventilation results in return of greater amounts of atmospheric gas which has not participated in gas exchange and has negligible CO\(_2\) to the atmosphere during exhalation. The end result is a decrease in mixed expired P\(_{CO_2}\) (P\(_{E_{CO_2}}\)) and an increase in the P\(_{ACO_2}\)-P\(_{E_{CO_2}}\) gradient. The fraction of tidal volume that occupies dead space (V\(_D/\)V\(_T\)) is calculated as follows:

\[ (P_{ACO_2} - P_{E_{CO_2}}) + P_{ACO_2} \]

Normal V\(_D/\)V\(_T\) is around 0.33. V\(_D/\)V\(_T\) increases in states that result in decreased pulmonary perfusion, such as pulmonary hypertension, hypovolemia, and decreased cardiac output. Venous admixture and intrapulmonary shunting predominantly affect oxygenation, resulting in a P\(_{AO_2}\)-P\(_{A_{CO_2}}\) (A-a\(_{CO_2}\)) gradient without elevation in P\(_{ACO_2}\). This is caused by the greater ventilation of perfused areas, which is sufficient to normalize P\(_{ACO_2}\) but not P\(_{AO_2}\) because of their respective dissociation curves (see Chapter 365). The relative straight-line relationship of hemoglobin-CO\(_2\) dissociation allows for averaging of P\(_{CO_2}\) from hyperventilated and hypoventilated areas. Because the association between oxygen tension and hemoglobin saturation plateaus with increasing P\(_{AO_2}\), the decreased hemoglobin-O\(_2\) saturation in poorly ventilated areas cannot be compensated for by well-ventilated areas where hemoglobin-O\(_2\) saturation has already reached near-maximum. This results in decreased arterial oxyhemoglobin saturation (Sa\(_{O_2}\)) and Pa\(_{O_2}\). Elevation of P\(_{ACO_2}\) in such situations is indicative of coincident alveolar hypoventilation. Examples of diseases leading to venous admixture include asthma and aspiration pneumonia, and those of intrapulmonary shunt include lobar pneumonia and ARDS.

**Diffusion**

Even if ventilation and perfusion are matched, gas exchange requires diffusion across the interstitial space between alveoli and pulmonary capillaries. Under normal conditions, there is sufficient time for the pulmonary capillary blood to equilibrate with alveolar gas across the interstitial space. When the interstitial space is filled with inflammatory cells or fluid, diffusion is impaired. Because the diffusion capacity of CO\(_2\) is 20 times greater than that of O\(_2\), diffusion defects manifest as hypoxemia rather than hypercarbia. Even with the administration of 100% oxygen, Pa\(_{O_2}\) increases to around 660 torr from 100 torr at sea level, and the concentration gradient for diffusion of O\(_2\) is increased by only 6.6 times. Therefore, with diffusion defects, lethal hypoxemia will set in before clinically significant CO\(_2\) retention results. In fact, in such situations P\(_{CO_2}\) is often decreased because of the hyperventilation that accompanies hypoxemia. Presence of hypercarbia in diseases that impair diffusion is indicative of alveolar hypoventilation from coexisting airway obstruction, exhaustion, or CNS depression. Examples of disease that impair diffusion are interstitial pneumonia, ARDS, scleroderma, and pulmonary lymphangiectasia.

**MONITORING A CHILD IN RESPIRATORY DISTRESS AND RESPIRATORY FAILURE**

**Clinical Examination**

It cannot be overemphasized that clinical observation is the most important component of monitoring. The presence and magnitude of abnormal clinical findings, their progression with time, and their temporal relation to therapeutic interventions serve as guides to diagnosis and management (see Chapter 373). As much as possible, the child with respiratory distress or failure should be observed in the position of greatest comfort and in the least threatening environment.

**Pulse oximetry** is the most commonly utilized technique to monitor oxygenation. Noninvasive and safe, it is the standard of care in bedside monitoring of children during transport, procedural sedation, surgery, and critical illness. It indirectly measures arterial hemoglobin-O\(_2\) saturation by differentiating oxyhemoglobin from deoxygenated hemoglobin using their respective light absorption at wavelengths of 660 nm (red) and 940 nm (infrared). A pulsatile circulation is required to enable detection of oxygenated blood entering the capillary bed. Percentage of oxyhemoglobin is reported as Sa\(_{O_2}\); however, the correct description is oxyhemoglobin saturation as measured by pulse oximetry (Sp\(_o_2\)). This is because Sp\(_o_2\) may not reflect Sa\(_{O_2}\) in certain situations. It is important to be familiar with the hemoglobin-O\(_2\) dissociation curve (see Chapter 373) in order to estimate Pa\(_{O_2}\) at a given oxyhemoglobin saturation. Because of the shape of the hemoglobin-O\(_2\) dissociation curve, changes in Pa\(_{O_2}\) above 70 torr are not readily identified by pulse oximetry. Also, at the same Pa\(_{O_2}\) level, there may be a significant change in Sp\(_o_2\) at a different blood pH value. In most situations, an Sp\(_o_2\) value greater than 95% is a reasonable goal, especially in emergency situations. There are exceptions, such as in patients with single ventricle cardiac lesions, in whom the pulmonary and systemic circulations are receiving blood flow from the same ventricle (e.g., after Norwood procedure for hypoplastic left heart syndrome), or with large left-to-right shunts (e.g., ventricular septal defect and patent ductus arteriosus). In these types of pathophysiologic situations, a lower Sp\(_o_2\)
is desired to avoid excessive blood flow to the lungs and pulmonary edema from the pulmonary vasodilatory effects of oxygen, and, in the patient with a single ventricle, diverting blood flow away from the systemic circulation. Because most commercially available pulse oximeters recognize all types of hemoglobin as either oxyhemoglobin or deoxygenated hemoglobin, they provide inaccurate information in the presence of carboxyhemoglobin and methemoglobin. In carbon monoxide poisoning, carboxyhemoglobin absorbs light in the same (red) wavelength as oxyhemoglobin, leading to overestimation of oxygen saturation. Methemoglobin absorbs light in both the oxygenated and deoxygenated wavelengths, which can cause either an overestimation or underestimation of oxygen saturation. Data suggests that increasing methemoglobin concentrations tend to drive $\text{SpO}_2$ toward 85%, no matter the actual percent of oxyhemoglobin. At lower methemoglobin levels, the pulse oximetry reading is falsely low, whereas high levels lead to a falsely high pulse oximetry reading. Newer pulse oximeters may have the ability to distinguish dыхемоглобинемias and to prevent false readings, but these are not currently in widespread use. It should be recognized that dangerous levels of hypercarbia may exist in patients with ventilatory failure, who have satisfactory $\text{SpO}_2$ if they are receiving supplemental oxygen. Pulse oximetry should not be the only monitoring method in patients with primary ventilatory failure, such as neuromuscular weakness and CNS depression. It is also unreliable in patients with poor perfusion and poor pulsatile flow to the extremities. Despite these limitations, pulse oximetry is a noninvasive, easily applicable, and effective means of evaluating the percentage of oxyhemoglobin in most patients.

Capnography (end-tidal CO$_2$ measurement) is helpful in determining the effectiveness of ventilation and pulmonary circulation. This method is especially useful for monitoring the level of ventilation in intubated patients. Diseases resulting in increased dead space or decreased pulmonary blood flow lead to decreases in end-tidal CO$_2$ and an overestimation of the adequacy of ventilation.

**Blood Gas Abnormalities in Respiratory Distress and Respiratory Failure**

Arterial blood gas analysis offers valuable assistance in diagnosis, monitoring, and management of a child in respiratory distress and failure. Because of technical difficulties in obtaining an arterial sample in children, a capillary blood gas (CBG) sample is most often obtained in emergency situations. A properly “arterialized” CBG sample obtained by warming the digit and obtaining free flowing blood is acceptable. The blood sample needs to be processed without delay. CBG provides a good estimate of $\text{PaCO}_2$ and arterial pH, but less so for $\text{PaO}_2$. In patients who mainly require monitoring of their ventilation (especially those whose oxygenation is being monitored with pulse oximetry) a venous blood gas sample provides a reliable estimate of arterial pH and $\text{PaCO}_2$ values, provided tissue perfusion is reasonably adequate. Venous $\text{PaCO}_2$ is approximtely 6 torr higher and pH approximately 0.03 lower than the arterial values. Venous $\text{PaO}_2$ has a poor correlation with $\text{PaO}_2$. Mixed venous $\text{O}_2$ saturation obtained from a central venous catheter in the right atrium is an excellent marker of the balance between oxygen delivery and oxygen consumption. In patients with a constant arterial $\text{O}_2$ content and $\text{O}_2$ consumption, mixed venous $\text{O}_2$ saturation offers valuable information regarding cardiac output.

Blood gas analysis is important not only for determining the adequacy of oxygenation and ventilation but also for determining site of the respiratory pathology and planning treatment (see Chapter 373). Briefly, in presence of pure alveolar hypoventilation (such as airway obstruction above the carina, decreased $\text{CO}_2$ responsiveness and neuromuscular weakness), the blood gas will show respiratory acidosis with an elevated $\text{Pco}_2$ but a relative sparing of oxygenation. V/Q mismatch (peripheral airway obstruction, bronchopneumonia) will be reflected in increased hypoxemia and variable levels of $\text{Pco}_2$ (low, normal, high) depending on severity of disease. Intrapulmonary right to left shunting and diffusion defects (alveolar-interstitial diseases such as pulmonary edema, ARDS) will be associated with a large A-a$\text{O}_2$ gradient and hypoxemia with relative sparing of $\text{CO}_2$ elimination unless there is coincident fatigue or CNS depression.

**Acid–Base Abnormalities in a Child with Respiratory Distress and Respiratory Failure**

It is crucial to analyze the magnitude and appropriateness of changes in pH, $\text{Pco}_2$ and bicarbonate ($\text{HCO}_3^-$) as they provide useful clues to the underlying pathophysiology and presence of more than one disorder. To do so, it is useful to assume baseline values of pH 7.40, $\text{Pco}_2$ 40 torr, and $\text{HCO}_3^-$ 24 mEq/L. Newborns have lower renal threshold for bicarbonate and therefore have slightly different baseline values of pH 7.38, $\text{Pco}_2$ 35 torr and $\text{HCO}_3^-$ 20 mEq/L.

**Metabolic Acidosis with Respiratory Compensation**

Patients with metabolic acidosis have decreased pH resulting from decreased serum bicarbonate. Chemoreceptor stimulation results in hyperventilation and respiratory compensation which may clinically manifest as respiratory distress. It should be recognized that a normal compensation does not completely correct the pH but rather minimizes a change in pH that would otherwise occur without compensation. The adequacy of respiratory compensation is judged by the extent of the decline in $\text{PaCO}_2$ in response to the decline in $\text{HCO}_3^-$ or pH. A normal compensation for metabolic acidosis results in a fall in $\text{Pco}_2$ by 1.2 torr for every 1 mEq/L fall in $\text{HCO}_3^-$. The most commonly used method to analyze the adequacy of respiratory compensation is the Winter’s formula: $\text{PaCO}_2 = (\text{HCO}_3^- × 1.5) + 8 ± 2$. A quick method is to look at the last 2 digits of pH (provided it is not below 7.10) which should be within 2 torr of $\text{Pco}_2$. For example, pH 7.27, $\text{Pco}_2$ 26 torr, and bicarbonate 12 mEq/L represents metabolic acidosis with a normal respiratory compensation response. On the other hand, pH 7.15, $\text{Pco}_2$ 30 torr, and $\text{HCO}_3^-$ 10 mEq/L constitutes metabolic acidosis with inadequate respiratory compensation. The reasons for inadequate compensation include decreased $\text{CO}_2$ responsiveness (e.g. narcotic poisoning, cerebral edema), abnormalities of lungs and airways, or neuromuscular weakness. A decrease in $\text{PaCO}_2$ that is greater than what could be expected as a normal compensatory response to metabolic acidosis is indicative of a mixed disorder. For example, a pH 7.20, $\text{Pco}_2$ 15 torr, and $\text{HCO}_3^-$ 7.5 mEq/L represents metabolic acidosis with a concomitant respiratory alkalosis because the decline in $\text{Pco}_2$ is greater than what can be expected as normal compensation. Combination of metabolic acidosis and respiratory alkalosis is often encountered in serious conditions such as cardiogenic shock (anxiety, stimulation of baroreceptors), sepsis, or toxic-metabolic states (salicylates, organic academia).

**Respiratory Acidosis with Metabolic Compensation**

Patients with respiratory acidosis have decreased pH as a result of elevated $\text{PaCO}_2$. An acute increase in $\text{Pco}_2$ of 10 torr results in a decrease in pH by 0.08. Thus, a child with severe status asthmaticus and a $\text{Pco}_2$ of 60 torr will have blood pH of around 7.24. Chronically elevated (greater than 3–5 days) $\text{Pco}_2$ is accompanied by renal compensation and increase in serum bicarbonate limiting the fall in pH to 0.03 for every 10 torr rise in $\text{Pco}_2$. Thus an infant with bronchopulmonary dysplasia who has a basal $\text{PaCO}_2$ of 60 torr will have blood pH around 7.34. These findings are helpful in distinguishing acute vs. chronic changes in $\text{PaCO}_2$. Also, for a given level of $\text{CO}_2$ accumulation, a decrease in pH that is greater than expected is indicative of concomitant metabolic acidosis and a decline in pH that is less than expected is due to accompanying metabolic alkalosis.

**Assessment of Oxygenation and Ventilation Deficits**

For standardizing management, following clinical progress, and determining prognosis for patients with defects in oxygenation or ventilation, various indicators have been proposed. Each one has its strengths and limitations:

- **A-a$\text{O}_2$ gradient**: Calculated by subtracting arterial $\text{Pao}_2$ from alveolar $\text{P}_a$ ($\text{P}_a = \text{Paco}_2 + \text{Pao}_2$). For the comparison to be valid, it must be at the same $\text{FiO}_2$.

- **$\text{Pao}_2$/$\text{FiO}_2$ ratio**: is calculated by dividing arterial $\text{Pao}_2$ by $\text{FiO}_2$. In hypoxic respiratory failure, a $\text{Pao}_2$/$\text{FiO}_2$ value <300 is consistent with acute lung injury, and a value <200 is consistent with ARDS.
Although the intent is to measure V/Q mismatch, intrapulmonary shunt, and diffusion defect, the status of alveolar hypoventilation could have a significant impact on PaO₂/Fio₂. PaO₂/PaO₂ is determined by dividing arterial PaO₂ by alveolar PaO₂. The level of alveolar ventilation is accounted for in the calculation of PaO₂. Therefore, PaO₂/PaO₂ is more indicative of V/Q mismatch and alveolar capillary integrity.

**Oxygenation index (OI)** is aimed at standardizing oxygenation to the level of therapeutic interventions such as mean airway pressure (MAP) and Fio₂, which are directed toward improving oxygenation. None of the previously mentioned indicators of oxygenation account for the degree of positive pressure respiratory support. OI is calculated as follows:

\[ OI = \left( \frac{MAP \times %O_2 \text{ inspired}}{Paco_2} \right) \]

The limitation of OI is that level of ventilation is not accounted for in the assessment.

**Ventilation index (VI)** is aimed at standardizing alveolar ventilation to the level of therapeutic interventions (such as peak inspiratory pressure [PIP] and ventilator rate) directed toward lowering Paco₂. VI is calculated as follows:

\[ VI = \left( \frac{\text{Ventilator Rate} \times (\text{PIP} - \text{PEEP}) \times \text{Paco}_2}{1000} \right) \]

### MANAGEMENT

The goal of management for respiratory distress and respiratory failure is to ensure a patent airway and provide necessary support for adequate oxygenation of the blood and removal of CO₂. Compared with hypercapnia, hypoxemia is a life-threatening condition; therefore, initial therapy for respiratory failure should be aimed at ensuring adequate oxygenation.

### Oxygen Administration

Supplemental oxygen administration is the least invasive and most easily tolerated therapy for hypoxic respiratory failure. **Nasal cannula** oxygen provides low levels of oxygen supplementation and is easy to administer. Oxygen is humidified in a bubble humidifier and delivered via nasal prongs inserted into the nares. In children, a flow rate <5 L/min is most often used because of increasing nasal irritation with higher rates. A common formula for an estimation of the Fio₂ during use of a nasal cannula in older children and adults is as follows:

\[ \text{Fio}_2 \% \text{O}_2 \text{ delivered} = 21\% + \left( \frac{\text{nasal cannula flow} \text{ (L/min)} \times 3}{} \right) \]

The typical Fio₂ value using this method is between 23% and 40%, although the Fio₂ varies according to the size of the child, the respiratory rate, and the volume of air moved with each breath. In a young child, because typical nasal cannula flows are a greater percentage of total minute ventilation, significantly higher Fio₂ may be provided. Alternately, a **simple mask** may be employed, which consists of a mask with open side ports and a valveless oxygen source. Variable amounts of room air are entrained through the ports and around the side of the mask, depending on the fit, size, and minute volume of the child. Oxygen flow rates vary from 5-10 L/min, yielding typical Fio₂ values between 0.30 and 0.65. If more precise delivery of oxygen is desired, other mask devices should be used.

A **Venturi mask** delivers preset fractions of oxygen through a mask and reservoir system by entraining precise amounts of room air into the reservoir with high-flow oxygen. The amount of room air entrainment and subsequent Fio₂ are determined by the adapter at the end of each mask reservoir. The adapter can be chosen to provide between 30% and 50% oxygen concentrations. Oxygen flow rates of 5-10 L/min are recommended to achieve desired Fio₂ and to prevent rebreathing. **Partial rebreather and nonrebreather** masks use a reservoir bag attached to a mask to provide higher fractions of oxygen. Partial rebreather masks have 2 open exhalation ports and contain a valveless oxygen reservoir bag. Some exhaled gas can mix with reservoir gas during exhalation, although most exits the mask via the exhalation ports. Through these ports, room air is also entrained during inspiration. A partial rebreather mask can provide up to 0.6 Fio₂ as long as oxygen flow is adequate to keep the bag from collapsing (typically 10-15 L/min). As with nasal cannulas, smaller children with smaller tidal volumes entrain less room air, and their Fio₂ values will be higher. Nonrebreather masks include 2 one-way valves, 1 between the oxygen reservoir bag and the mask and 1 on 1 of the 2 exhalation ports. This arrangement minimizes mixing of exhaled and fresh gas and entrainment of room air during inspiration. The second exhalation port has no valve, a safeguard to allow some room air to enter the mask in the event of disconnection from the oxygen source. A nonrebreather mask can be useful in conjunction with an oxygen blender allows delivery of fractions of oxygen between 0.50 and 0.95. When supplemental oxygen alone is inadequate to improve oxygenation, or when ventilation problems coexist, additional therapies may be necessary.

### Airway Adjuncts

Maintenance of a patent airway is a critical step in maintaining adequate oxygenation and ventilation. Artificial pharyngeal airways may be useful in patients with oropharyngeal or nasopharyngeal airway obstruction and in those with neuromuscular weakness in whom native extrathoracic airway resistance contributes to respiratory compromise. An **oropharyngeal airway** is a stiff plastic spacer with grooves along each side that can be placed in the mouth to run from the teeth along the tongue to its base just above the vallecula. The spacer prevents the tongue from opposing the posterior pharynx and occluding the airway. Because the tip sits at the base of the tongue, it is usually not tolerated by patients who are awake or whose gag reflex is strong. The **nasopharyngeal airway**, or nasal trumpet, is a flexible tube that can be inserted into the nose to run from the nasal opening along the top of the hard and soft palate with the tip ending in the hypopharynx. It is useful in bypassing obstruction from enlarged adenoids or from contact of the soft palate with the posterior nasopharynx. Because it is inserted past the adenoids, a nasopharyngeal airway should be used with caution in patients with bleeding tendencies.

### Inhaled Gases

**Helium-oxygen mixture (heliox)** is useful in overcoming airway obstruction and improving ventilation. Helium is much less dense and slightly more viscous than nitrogen. When substituted for nitrogen, helium helps maintain laminar flow across an obstructed airway, decreases airway resistance, and improves ventilation. It is especially helpful in diseases of large airway obstruction in which turbulent airflow is more common, such as acute laryngotracheobronchitis, subglottic stenosis, and vascular ring. It is also used in patients with severe status asthmaticus. To be effective, helium should be administered in concentrations of at least 60%, so associated hypoxemia may limit its use in patients requiring more than 40% oxygen. **Nitric oxide (NO)** is a powerful inhaled pulmonary vasodilator. Its use may improve pulmonary blood flow and V/Q mismatch in patients with diseases that elevate pulmonary vascular resistance, such as persistent pulmonary hypertension of the newborn, primary pulmonary hypertension, and secondary pulmonary hypertension as a result of chronic excess pulmonary blood flow (e.g., ventriculopectal defect) or collagen vascular diseases. NO is administered in doses ranging from 5-20 parts per million. Although administration of NO to unintubated patients is possible, it is usually administered to patients receiving mechanical ventilation through endotracheal tubes, because of the need for precision in NO dosing.

### Positive-Pressure Respiratory Support

Noninvasive positive-pressure respiratory support is useful in treating both hypoxemic and hypoventilatory respiratory failure. Positive airway pressure helps aerate partially atelectatic or filled alveoli, prevent alveolar collapse at end exhalation, and increase functional residual capacity (FRC). This improves pulmonary compliance and hypoxemia and decreases intrapulmonary shunt. In addition, positive pressure ventilation is useful in preventing collapse of extrathoracic airways by maintaining positive airway pressure during inspiration. Improving compliance and overcoming airway resistance also improves tidal volume and, therefore, ventilation. **A high-flow nasal cannula** delivers
gas flow at 4-16 L/min, providing significant continuous positive airway pressure (CPAP). The amount of CPAP provided is not quantifiable and varies with each patient, depending on the percentage of total inspiratory flow that is delivered from the cannula, airway anatomy, and degree of mouth breathing. In small children, the relative amount of CPAP for a given flow is usually greater than in older children, and may provide significant positive pressure. The FiO₂ can be adjusted by provision of gas flow through an oxygen blender. Another benefit of a high-flow nasal cannula system is the washout of CO₂ from the nasal pharynx, which decreases rebreathing of CO₂ and dead space ventilation. For delivery of high-flow air or oxygen, adequate humidification is essential and is achieved with use of a separate heated humidification chamber. CPAP can also be provided through snugly fitting nasal prongs or a tight-fitting facial mask attached to a ventilator or other positive-pressure device. Noninvasive CPAP is most useful in diseases of mildly decreased lung compliance and low FRC, such as atelectasis and pneumonia. Diseases of extrathoracic airway obstruction in which extrathoracic negative airway pressures during inspiration lead to airway narrowing (e.g., laryngotracheitis, obstructive sleep apnea, postextubation airway edema) may also benefit from CPAP. Potential risks include nasal irritation, hyperinflation from excessive CPAP in smaller patients, and abdominal distention from swallowed air.

**Bilevel positive airway pressure (BiPAP)** machines provide positive airway pressure during exhalation and additional positive pressure during inspiration. A BiPAP device allows one to set an expiratory positive airway pressure and an inspiratory positive airway pressure. The additional positive pressure during inspiration helps augment tidal volume and improve alveolar ventilation in low compliance and obstructive lung disease. The inspiratory and expiratory pressures can be adjusted independently to suit individual needs and comfort. Because of the additional support during inspiration, patients with neuromuscular weakness in particular tend to benefit from BiPAP support. BiPAP may also be helpful in diseases of intrathoracic airway obstruction. During exhalation, expiratory positive airway pressure can decrease the effects of airway closure by raising intraluminal pressure and ameliorating intrathoracic airway collapse. During inspiration, inspiratory positive airway pressure can unload inspiratory muscles, and decrease work of breathing (Fig. 71-2).

### Endotracheal Intubation and Mechanical Ventilation

When hypoxemia or significant hypoventilation persists despite the interventions already described, tracheal intubation and mechanical ventilation are indicated. Additional indications for intubation include maintaining airway patency in patients who have the potential for airway compromise, such as those with actual or potential neurolologic deterioration, and in patients with hemodynamic instability. Proper monitoring is essential to ensuring a safe and successful tracheal intubation. Pulse oximetry, heart rate, and blood pressure monitoring are mandatory and should be forgone only in situations calling for emergency intubation. All necessary equipment, including bag-mask ventilation device, laryngoscope, tracheal tube with stylet, and suction equipment, must be available and working properly prior to initiation of intubation. The proper internal diameter (ID) for the tracheal tube can be estimated using the following formula:

\[
\text{ID} = (\text{Age [yr]}/4) + 4
\]

Table 71-9 provides average values for age, size, and depth of insertion for tracheal tubes. Preoxygenation of the patient with high fractions of inspired oxygen is essential and will allow maximum procedure time prior to the onset of hypoxemia.

Although intubation can be accomplished without sedation and pharmacologic paralysis in selected patients, the physiologic benefits of these measures to the patient as well as to the facilitation of the intubation usually far outweigh the risks; sedation and paralysis should be considered standard unless contraindicated. Administration of a sedative and analgesic followed by a paralytic agent is a common pharmacologic regimen for facilitating intubation. The particular type and dose of each agent often depends on the underlying disease and clinician preference. Table 71-10 lists commonly used agents. An alternative to this pharmacologic approach, especially when intubation is urgent or the patient is suspected of having a full stomach, increasing the risk of aspiration, is rapid sequence intubation (see Chapter 67).

Once adequate sedation and/or paralysis have been achieved, ventilation should be assisted with a bag-mask device. After optimal

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**Figure 71-2** Work of breathing (WOB) in status asthmaticus with and without noninvasive positive pressure ventilation. In the expiratory limb of the respiratory cycle, the equal pressure point is displaced distally, causing airways to begin to close at a higher lung volume (increased closing capacity), leading to dynamic hyperinflation, and autopositive end-expiratory pressure (auto-PEEP) (**A**). Application of expiratory positive airway pressure stents the airways, reducing intrathoracic airway collapse, dynamic hyperinflation, auto-PEEP (**B**), and WOB. In the inspiratory limb, the patient needs to generate less negative pressure to initiate inspiration because of lower autopermissive end-expiratory pressure. Inspiratory muscles are further unloaded by inspiratory positive airway pressure (IPAP) throughout inspiration for the given tidal volume. Both expiratory and inspiratory WOB are thus reduced by application of noninvasive positive pressure ventilation. (From Samaik AA, Samaik AP: Noninvasive ventilation in pediatric status asthmaticus: Sound physiologic rationale but is it really safe, effective, and cost-efficient? Pediatr Crit Care Med 13:484–485, 2012.)
preoxygenation, intubation can be performed. The clinician uses his/ her dominant hand to open the patient’s mouth and inserts the laryngoscope blade gently along the tongue to its base. The airway opening can be visualized by applying lift up and away from the clinician, along the axis of the laryngoscope handle. If a straight (Miller) laryngoscope blade is used, the epiglottis is lifted anteriorly by the tip of the blade to visualize the glottis. If a curved (Macintosh) blade is used, the tip should be advanced into the vallecula and then lifted to visualize the glottis. Secretions often obscure visualizations at this step and should be suctioned clear. Once clear visualization of the vocal cords is accomplished, the tube can be placed through the cords. Rapid confirmation of tube placement is essential and should be assessed by all of the following steps as possible: Auscultation of both lung fields as well as the epiglottis for equal breath sounds and good air movement and evaluation of the abdomen for increasing distention should be performed. Adequate bilateral chest expansion and misting inside the tracheal tube with each breath are suggestive of proper tube placement. An increasing heart rate, if heart rate has decreased during the attempt, and a rising or normal pulse oximetry reading are suggestive of successful tube placement. Preoxygenation may significantly delay a drop in SpO2 with improper tube placement, leading to a significant delay in its recognition. Confirmation of exhaled CO₂ is mandatory. It can be accomplished with use of a disposable colorimetric CO₂ detector or with capnography. In situations of very low pulmonary perfusion, such as cardiac arrest, exhaled CO₂ may not be detected. A chest radiograph should also be obtained to confirm proper placement of the tracheal tube, which should lie roughly halfway between the glottis and the carina (see Chapter 62).

**Transient Manual Ventilation in the Immediate Preintubation and Postintubation Periods**

Establishment of ventilation via bag and mask or bag and tracheal tube is required prior to transport of the patient to a setting of continued critical care. The technique of manual ventilation should take into account the underlying pathology. Ventilation of patients with diseases characterized by low FRC (pneumonia, pulmonary edema, ARDS, etc.) should include the application of positive end-expiratory pressure (PEEP) to prevent alveolar derecruitment. This can be accomplished with use of a PEEP valve on a self-inflating ventilation bag or by careful manipulation of exhaust gas using an anesthesia bag. Such diseases are also characterized by a short time constant and therefore are best managed with relatively small tidal volumes and high ventilation rates.

Diseases characterized by airway obstruction have prolonged time constants and are therefore best managed with relatively slow rates and high tidal volumes.

**Bibliography** is available at Expert Consult.

71.1 Mechanical Ventilation

Ashok P. Sarnaik and Christopher Mastropietro

The decision to institute mechanical ventilation is based mainly on the need to assist lung function; supporting left ventricular performance and treating intracranial hypertension are additional indications. Although there are no absolute criteria for derangement of gas exchange, Pao₂ < 60 torr while breathing > 60% oxygen, Paco₂ > 60 torr, and pH < 7.25 are often reasons to initiate mechanical ventilation. Clinical impressions of fatigue and impending exhaustion are also indications for ventilatory support even in the presence of adequate gas exchange. Positive-pressure ventilation is a powerful means of decreasing left ventricular afterload, and it is used for this purpose in patients with cardiogenic shock resulting from left ventricular dysfunction. Mechanical ventilation is also used in patients whose respirations are unreliable (e.g., unconscious patients, those with neuromuscular dysfunction) and when deliberate hyperventilation is desired, such as in patients with intracranial hypertension.

Mechanical ventilation neither is intended to normalize gas exchange nor is a form of cure. The goals are to maintain sufficient oxygenation and ventilation to ensure tissue viability until the disease process has resolved and to minimize the inevitable complications of the therapeutic intervention itself. Pao₂, Paco₂, and pH levels are maintained in ranges that provide a safe environment for the patient while protecting the lungs from damage due to oxygen toxicity, pressure (barotrauma), tidal volume overdistention (volutrauma), atelectrauma, and cytokine release (biotrauma) (Figs. 71-3 and 71-4).

**Basic Concepts of Ventilator Management**

**Equation of Motion**

A pressure gradient is required for air to move from one place to another (Fig. 71-5). During natural spontaneous ventilation, inspiration results from generation of negative intrapleural pressure from

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### Table 71-10 Medications Commonly Used for Intubation

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>ONSET (min)</th>
<th>DURATION (min)</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedatives/anesthetics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.1 mg/kg IV</td>
<td>3-5</td>
<td>60-120</td>
<td>Amnesia</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.1 mg/kg IV</td>
<td>3-5</td>
<td>120-240</td>
<td>Respiratory depression</td>
</tr>
<tr>
<td>Ketamine</td>
<td>1-2 mg/kg IV</td>
<td>2-3</td>
<td>10-15</td>
<td>Respiratory depression</td>
</tr>
<tr>
<td>Propofol</td>
<td>1-3 mg/kg IV</td>
<td>0.5-2</td>
<td>10-15</td>
<td>Bronchodilation</td>
</tr>
<tr>
<td>Thiopental</td>
<td>4-7 mg/kg IV</td>
<td>0.5-1</td>
<td>5-10</td>
<td>Apnea</td>
</tr>
<tr>
<td>Analgesics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>2.5 µg/kg IV</td>
<td>3-5</td>
<td>30-90</td>
<td>Respiratory depression</td>
</tr>
<tr>
<td>Morphine</td>
<td>0.1 mg/kg IV</td>
<td>5-15</td>
<td>120-240</td>
<td>Chest wall rigidity</td>
</tr>
<tr>
<td>Neuroromuscular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>blocking agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vecuronium</td>
<td>0.1 mg/kg IV</td>
<td>2-3</td>
<td>30-75</td>
<td>Respiratory depression</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>0.6-1.2 mg/kg IV</td>
<td>5-15</td>
<td>15-60</td>
<td>Renal elimination</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>0.1 mg/kg IV</td>
<td>2-3</td>
<td>25-30</td>
<td>Renal elimination</td>
</tr>
</tbody>
</table>

BP, blood pressure; HR, heart rate; ICP, intracranial pressure; IM, intramuscularly; IV, intravenously.
Bibliography


Chapter 71: Respiratory Distress and Failure

1. Pressure gradient is required to move air from one place to another.
2. Movement of air is opposed by flow-resistive and elastic properties of the system.

\[
\text{Pressure gradient} = \frac{\Delta \text{volume}}{\text{compliance}} + \left( \text{Flow} \times \text{resistance} \right)
\]

Elastic properties

Flow-resistive properties

contraction of the diaphragm and intercostal muscles, drawing air from the atmosphere across the airways into the alveoli. During mechanical ventilation, inspiration results from positive pressure created by compressed gases through the ventilator, which pushes air across the airways into alveoli. In both spontaneous and mechanical ventilation, exhalation results from alveolar pressure generated by the elastic recoil of the lung and the chest wall. Pressure necessary to move a given amount of air into the lung is determined by 2 factors: lung and chest wall elastance, and airway resistance. Figure 71-5 describes the relationship among pressure gradient, compliance, and resistance. Elastance—defined as the change in pressure (ΔP) divided by the change in volume (ΔV)—refers to the property of a substance to oppose deformation. It is opposite of compliance (ΔV + ΔP), the property of a substance to allow distention or lengthening when subjected to pressure. Compliance (C) is therefore expressed as 1/elastance.

The pressure needed to overcome tissue elastance is measured in conditions in which there is no flow (at end-inspiration and end-expiration) and is therefore a reflection of static conditions in the lung. It is influenced by tidal volume and compliance (P = ΔV + C). It is increased with high tidal volume and low compliance. This pressure gradient is used to calculate the static compliance of the respiratory system (C_{stat}).

Resistance (R) refers to the opposition to generation of flow. It is measured as the amount of pressure needed to generate a unit of flow (ΔP + ΔF). Pressure needed to overcome airway resistance is calculated as flow multiplied by resistance. Because this pressure is needed only when the flow is occurring through the airways, it is referred to as the dynamic component. Pressure to overcome flow-resistive properties is measured when there is maximum flow and is therefore under dynamic conditions. It is increased in conditions with greater airway resistance and flow rate. Flow rate depends on the time allowed for inspiration and expiration. At higher respiratory rates, there is less time available for each inspiration and expiration, necessitating higher flows; therefore higher pressure is required to overcome flow-resistive properties. The pressure gradient necessary to move air from one place to another is the sum of pressure needed to overcome the elastic and flow-resistive properties of the lung. This pressure gradient is taken into
account to calculate the dynamic compliance of the respiratory system (Cdyn). The difference in change in pressure between static conditions and dynamic conditions is attributable to airway resistance.

**Functional Residual Capacity**
Also see Chapter 373.
During inspiration, oxygen-enriched gas enters alveoli. During exhalation, oxygen continues to be removed by the pulmonary capillary circulation. FRC is the volume of gas left in the alveoli at the end of expiration. It is the only source of gas available for gas exchange during exhalation. In diseases with decreased FRC (e.g., ARDS, pulmonary edema), alveolar oxygen concentration declines sharply throughout expiration, resulting in hypoxemia. Two ventilator strategies commonly employed to improve oxygenation in such situations are the application of PEEP and increasing the inspiratory time (Ti) (Fig. 71-6). PEEP increases FRC, whereas a longer Ti allows longer exposure of pulmonary capillary blood to a higher concentration of O2 during inspiration.

**Time Constant**
At the beginning of inspiration, the atmospheric pressure is higher than the pressure in the alveoli, resulting in movement of air into the alveoli. During mechanical ventilation, the ventilator circuit serves as the patient's atmosphere. As alveoli expand with air, the alveolar pressure rise throughout inspiration until it equilibrates with the ventilator pressure, at which time airflow ceases. Expiration starts when the ventilator pressure falls below the alveolar pressure. Alveolar pressure decreases throughout expiration until it reaches the ventilator pressure, at which time no further egress of air from the alveoli occurs. If inspiration or expiration is terminated before pressure equilibration between alveoli and the ventilator is allowed to occur, alveolar expansion during inspiration or alveolar emptying during expiration is incomplete. Incomplete inspiration results in delivery of decreased tidal volume, whereas incomplete expiration is associated with air trapping and the presence of residual PEEP in the alveoli that is greater than the ventilator pressure, referred to as auto-PEEP. Some time is required for pressure equilibration to occur between alveoli and the atmosphere, which is reflected in the time constant (TC). It takes 3 TCs for 95%, and 5 TCs for 99%, of pressure equilibration to occur. The TC depends on compliance and resistance, and their relationship is depicted in Figure 71-7.

Diseases with decreased compliance (increased elastance) are characterized by high elastic recoil pressure, which results in more rapid equilibration of alveolar and ventilator pressures, thereby decreasing TC. Diseases with increased airway resistance are associated with slower flow rates, require longer time for movement of air from one place to another, and therefore have increased TC. Airways expand during inspiration and narrow during expiration (see Chapter 373). Therefore, expiratory time constant (TCe) is longer than inspiratory time constant (TCi). In intrathoracic airway obstruction (asthma, bronchiolitis, aspiration syndromes), airway narrowing is much more pronounced during expiration. Therefore, although both TCe and TCi are prolonged in such diseases, TCi is much more prolonged than TCe. Patients with such diseases therefore are best ventilated with slower rates, higher tidal volume, and longer expiratory time than inspiratory time. In diseases characterized by decreased compliance, both TCe and TCi are short; however, the TCe is closer to TCi than in normal lungs because of the stiffer alveoli recoil with greater force. Patients with these diseases are best ventilated with small Vt to prevent ventilator-induced lung injury and with a relatively longer inspiratory time in each breath to improve oxygenation.

**Critical Opening Pressure**
Collapsed or atelectatic alveoli require a considerable amount of pressure to open. Once open, the alveoli require relatively less pressure for continued expansion. The process of opening atelectatic alveoli is called recruitment. In a normal lung, alveoli remain open at the end of expiration, and therefore the lung requires relatively less pressure to receive its tidal volume. In a disease process in which the alveoli...
collapse at the end of expiration (e.g., ARDS), a substantial amount of pressure is required to open the alveoli during inspiration. This pressure causes ventilator-induced lung injury via 2 mechanisms: (1) barotrauma at the terminal airway–alveolar junction and (2) volutrauma as a result of overdistention of alveoli that are already open (see Figs. 71-3 and 71-4). Although a pulmonary parenchymal disease process is rarely uniform, and each of the millions of alveoli may have its own mechanical characteristics, a composite volume-pressure relationship could be conceptualized for the whole lung (Fig. 71-8).

In these situations, the lower and upper portions of the curve are relatively horizontal, and the middle portion is more vertical. At the beginning of inspiration, atelectatic alveoli are being recruited, requiring high pressure for a relatively small increase in volume. Once they are recruited, further increase in volume requires relatively less pressure. The pressure at which most alveoli are open is called critical opening pressure; this point is also referred to as the lower inflection point (lower P_{FLEX}). After the lower P_{FLEX}, greater volume can be delivered for relatively less pressure until the upper P_{FLEX} is reached, at which the volume-pressure curve again becomes relatively horizontal. The goal of mechanical ventilation in alveolar interstitial pathology is to deliver a tidal volume between the lower and upper inflection points, the so-called safe zone of ventilation. If V_t is delivered with a change in inflation pressure that includes the lower P_{FLEX}, alveoli are likely to open and close during every breath, a process termed tidal recruitment that is injurious to the lung, especially at the terminal airway–alveolar junction. If V_t is delivered with a change of pressure that includes the upper P_{FLEX} overdistention of alveoli is likely to occur, resulting in volutrauma and barotrauma. Keeping tidal ventilation between the upper and lower P_{FLEX} values is accomplished by maintaining a level of PEEP to produce baseline alveolar recruitment and delivering a relatively small (6 mL/kg) V_t. Termed “open lung” strategy, this approach has proved to be beneficial in alveolar interstitial diseases such as ARDS.

**PHASES OF MECHANICAL VENTILATION**

The planning of a ventilatory strategy must consider the four phases of the respiratory cycle separately, taking into account these patient clinical characteristics: (1) initiation of respiration and a variable that is controlled, often referred to as mode; (2) inspiratory phase characteristics, which determine the duration of inspiration and how the pressure or volume is delivered; (3) termination of inspiration, often referred to as cycle; and (4) expiratory phase characteristics. Ideally, mechanical ventilation should not completely take over the work of breathing but, rather, should assist the patient’s own respiratory effort. In the absence of the patient’s effort, respiratory muscle deconditioning may occur, making weaning from mechanical ventilation more difficult.

### Initiation of Inspiration and the Control Variable (Mode)

The initiation of inspiration may be set to occur at a predetermined rate and interval regardless of patient effort, or it could be timed in response to patient effort. Once inspiration is initiated, the ventilator breath either is controlled entirely by the ventilator (control mode) or supports the patient’s inspiratory effort to a predetermined inspiratory volume or pressure target (support mode). Advances in technology allow for greater patient–ventilator synchrony to occur. The ventilator may be set to be “triggered” by the signal it receives as a result of patient effort. This may be in the form of lowering of either pressure (pressure trigger) or airflow (flow trigger) in the ventilator circuit generated by the patient’s inspiratory effort. If no such signal is received because of lack of patient effort, the ventilator delivers a breath at an interval selected by the operator.

### Control Modes - Intermittent Mandatory Ventilation Mode

In intermittent mandatory ventilation (IMV), the inspiration is initiated at a set frequency with a timing mechanism independent of patient effort. In between machine-delivered breaths, the patient can breathe spontaneously from a fresh source of gas. IMV allows for adjustment of ventilator support according to the patient’s needs, making it useful in the weaning process. Lack of synchrony between machine-delivered breaths and patient efforts may result in ineffective ventilation and patient discomfort, especially when IMV is delivered at a high rate. In such cases, the patient may require sedation and pharmacologic paralysis for efficient delivery of tidal volume. To obviate this problem, *synchronized IMV* (SIMV) is used, whereby the machine-delivered breaths are triggered by the patient’s inspiratory efforts (Fig. 71-9). In between the machine-delivered breaths, a fresh source of gas is available for spontaneous patient breaths. In the
absence of patient effort, the patient receives a backup rate much like in IMV mode. Even with SIMV, ventilator–patient asynchrony can occur, because Vt, inflation pressure, and inspiratory time are determined by the ventilator alone.

**Assist-Control Mode**

In assist-control (AC) mode, each and every patient breath is triggered by pressure or flow generated by patient inspiratory effort and “assisted” with either preselected inspiratory pressure or volume. The rate of respirations is therefore determined by the patient's inherent rate. A backup total (patient and ventilator) obligatory rate is set to deliver a minimum number of breaths. On AC mode with a backup rate of 20 breaths/min, all of the breaths of a patient with an inherent respiratory rate of 15 breaths/min will be assisted by the ventilator, and the patient will receive 5 additional breaths/min. On the other hand, a patient with an inherent rate of 25 breaths/min will receive all 25 breaths assisted. Although useful in some patients, the AC mode cannot be used in the weaning process, which involves gradual decrease in ventilator support.

**Control Variable**

Once initiated, either the tidal volume or the pressure delivered by the machine can be controlled. The machine-delivered breath is thus referred to as either volume-controlled or pressure-controlled (Table 71-11).

With volume-controlled ventilation (VCV), machine-delivered volume is the primary control, and the inflation pressure generated depends on the respiratory system's compliance and resistance. Changes in respiratory system compliance and resistance are therefore easily detected from changes observed in inflation pressure. In pressure-controlled ventilation (PCV), the pressure change above the baseline is the primary control, and the tidal volume delivered to the lungs depends on the respiratory system's compliance and resistance. Changes in respiratory system compliance and resistance do not affect inflation pressure and may therefore go undetected unless the exhaled Vt is monitored. VCV and PCV have their own advantages and disadvantages (see Table 71-11). Generally speaking, PCV is more efficient than VCV in terms of amount of tidal volume delivered for a given inflation pressure during ventilation of a lung that has nonuniform time constants, such as asthma. In VCV, relatively less-obstructed airways are likely to receive more of the machine-delivered volume throughout inspiration than relatively more-obstructed airways with longer time constants (Fig. 71-10A). This situation would result in uneven ventilation, higher PIP, and a decrease in dynamic compliance. In PCV, because of a constant inflation pressure that is held throughout inspiration, relatively less-obstructed lung units with shorter time constants would achieve pressure equilibration earlier during inspiration than the relatively more-obstructed areas. Thus, units with shorter TCs would attain their final volume earlier in inspiration, and those with longer TCs would continue to receive additional volume later in inspiration (Fig. 71-10B). This situation would result in more even distribution of inspired gas, delivery of more Vt for the same inflation pressure, and improved dynamic compliance in comparison with VCV.

**Pressure-regulated volume control (PRVC)** combines the advantages of VCV and PCV. In this mode, the Vt and Ti are controlled as primary variables but the ventilator determines the amount of pressure needed to deliver the desired Vt. Inflation pressure is thus adjusted to deliver the prescribed Vt over the Ti, depending on the patient's respiratory compliance and resistance.

**Support Modes**

Pressure-support ventilation (PSV) and volume-support ventilation (VSV) are designed to support the patient’s spontaneous respirations. With PSV, initiation of inspiration is triggered by the patient's spontaneous breath, which is then “supported” by a rapid rise in ventilator pressure to a preselected level. The inspiration is continued until the inspiratory flow rate falls to a set level (generally 25% of peak flow rate) as the patient's lungs fill up. Thus, Ti is controlled by the patient's own efforts. PSV can be combined with SIMV so that any breath above the SIMV rate is supported by PSV. Allowing the patient to control as much of the rate, Vt, and inspiratory time as possible is considered a gentler form of mechanical ventilation than SIMV, in which the Vt (or inflation pressure) and Ti are preset. PSV as the sole source of mechanical ventilator support is often not adequate for patients with severe lung disease; however, it is especially useful in patients in the process of being weaned and in patients who require mechanical ventilation for relatively minor lung disease or for neuromuscular weakness. VSV is similar to PSV, in that all the spontaneous breaths are supported. In VSV, inspiratory pressure to support spontaneous breaths is adjusted to guarantee a preset Vt. If there is a change in respiratory mechanics or patient effort, the inspiratory pressure to support the breath initiated by patient effort is automatically adjusted to deliver the set Vt.

**Inspiratory Phase Characteristics**

Ti, inspiratory flow waveform, and pressure rise time can be adjusted in the inspiratory phase to suit the patient's respiratory mechanics. In PCV, the duration of Ti is directly set in seconds. In VCV, the inspiratory time can be adjusted by adjusting the inspiratory flow (volume/time). The choice of Ti value depends on the respiratory rate, which determines the total duration of each breath, and on the estimation of inspiratory and expiratory time constants. Decreasing the flow rate delivery increases Ti, and vice versa. With an increase in Ti, the pulmonary capillary blood is exposed to a higher level of alveolar Pao2 for a longer time. This is beneficial in diseases with decreased FRC, such as ARDS and pulmonary edema. An increase in Ti also increases

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### Table 71-11: Characteristics of Pressure-Controlled and Volume-Controlled Methods of Ventilation

<table>
<thead>
<tr>
<th></th>
<th>PRESSURE-CONTROLLED VENTILATION</th>
<th>VOLUME-CONTROLLED VENTILATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control setting(s)</td>
<td>Inflation pressure</td>
<td>Vt</td>
</tr>
<tr>
<td></td>
<td>Inspiratory time</td>
<td>Flow rate</td>
</tr>
<tr>
<td></td>
<td>Rise time</td>
<td>Inspiratory flow pattern</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(constant vs decelerating)</td>
</tr>
<tr>
<td>Machine-delivered volume</td>
<td>Depends on respiratory system</td>
<td>Constant</td>
</tr>
<tr>
<td></td>
<td>compliance and resistance</td>
<td></td>
</tr>
<tr>
<td>Inflation pressure</td>
<td>Constant</td>
<td>Depends on respiratory system</td>
</tr>
<tr>
<td></td>
<td></td>
<td>compliance and resistance</td>
</tr>
<tr>
<td>Endotracheal tube leak</td>
<td>Somewhat compensated</td>
<td>Leaked volume part of Vt</td>
</tr>
<tr>
<td>Distribution of ventilation</td>
<td>More uniform in lungs with</td>
<td>Less uniform in lungs with</td>
</tr>
<tr>
<td></td>
<td>varying time constant units</td>
<td>varying time constant units</td>
</tr>
<tr>
<td>Patient comfort</td>
<td>Possibly compromised</td>
<td>Possibly enhanced</td>
</tr>
<tr>
<td>Weaning</td>
<td>Inflation pressure adjustment</td>
<td>Vt remains constant, inflation</td>
</tr>
<tr>
<td></td>
<td>required to deliver desired Vt</td>
<td>pressure automatically</td>
</tr>
<tr>
<td></td>
<td></td>
<td>weaned</td>
</tr>
</tbody>
</table>

Vt, tidal volume.
that even a brief disconnection from a ventilator, and therefore having 
eases and thereby improve oxygenation. There is growing recognition 
alveoli and to increase FRC in patients with alveolar–interstitial dis 
most important clinical benefits of PEEP are to recruit atelectatic 
the inspiratory flow decreases below a certain percentage (usually 25%) 
barotrauma. The inspiration-terminating mechanism is set somewhat 
mechanical breath, inspiration is terminated after a preselected T 
Control modes are time-cycled and volume-cycled. With a time-cycled 
tion. It is debatable which flow pattern is better for a given disease. In 
maximum at the start of inspiration and declines throughout its dura 
throughout inspiration. In a descending ramp waveform, the flow is 
early inspiration: Areas with short time constants fill 

Termination of Inspiration (Cycle)
The two most commonly used inspiratory terminating mechanisms in 
control modes are time-cycled and volume-cycled. With a time-cycled 
ception is terminated after a preselected Ti has elapsed, whereas with volume-cycled breath, the inspiration ends after 
with the PIP held constant for the duration of inspiration. A volume- 
cycled breath can be pressure-limited as a safety mechanism to avoid 
the inspiration-terminating mechanism is set somewhat 
different in support modes. In PSV, the inspiration is set to end after 
the inspiratory flow decreases below a certain percentage (usually 25%) 
peak inspiratory flow. This happens when the patient no longer 
desires to receive additional VT. Such a breath can be termed flow- 
cycled. In volume support mode, inspiration is terminated when the 
patient has received the desired VT.

Expiratory Phase Maneuvers
The most useful expiratory phase maneuver is the application of PEEP, 
which is applied to both the control breath and the assisted breath. The 
most important clinical benefits of PEEP are to recruit atelectatic 
alveoli and to increase FRC in patients with alveolar–interstitial dis 
ees and thereby improve oxygenation. There is growing recognition 
that even a brief disconnection from a ventilator, and therefore having 
zero end-expiratory pressure, can result in significant alveolar dere 
rentment and decline in oxygenation. In patients with obstructive 
lesions in which insufficient exhalation results in air trapping and auto 
PEEP, extrinsic PEEP (that applied through a mechanical device) can 
prevent airway closure during expiration and improve ventilation. 
Other salutary effects of PEEP include redistribution of extravascular 
lung water away from gas-exchanging areas, improved ventilation– 
perfusion relationship, and stabilization of the chest wall. The effect of 
PEEP on lung compliance is variable, depending on the level of PEEP 
provided and the patient’s pulmonary mechanics. By shifting the VT 
to a more favorable part of the pressure-volume curve, PEEP may recruit more alveoli, delay airway closure, and improve lung 
compliance. Excessive PEEP, on the other hand, may lead to overd 
tension of alveoli and reduced compliance. The effect of PEEP in ind 
vidual patients can be ascertained by measuring exhaled VT and 
calculating dynamic compliance. Other deleterious effects of PEEP 
include decreased venous return, increased pulmonary vascular resis 
tance, and decreased cardiac output.

Additional Ventilatory Modalities
Airway Pressure Release Ventilation
Airway pressure release ventilation (APRV) improves oxygenation in 
cases of severe hypoxic respiratory failure resulting from alveolar– 
interstitial disease. This modality applies a CPAP, designated CPAPHIGH, 
to recruit and maintain FRC with brief intermittent release phases of 
CPAPLOW to allow alveolar gas to escape. CPAPHIGH is analogous to PIP, 
and CPAPLOW is similar to setting PEEP. In contrast to the patient 
receiving conventional mechanical ventilation, a patient receiving 
APRV spends the majority of time in the CPAPHIGH phase, which may 
last as long as 3-5 sec with a brief (0.3-0.5 sec) time in the CPAPLOW. 
These atypically long inspiratory times are tolerated because of a 
floating expiratory valve in the ventilator circuit that permits spont 
aneous breathing during CPAPHIGH phase. Therefore, even if CPAPHIGH 
phase can be considered inspiratory and CPAPLOW phase can be con 
sidered expiratory as far as the ventilator is concerned, the patient is 
able to breathe spontaneously during both of these phases. The longer 
ventilator inspiratory times recruit lung units, and the ability to breathe 
spontaneously during this phase allows distribution of gas flow to 
atelectatic lung regions. The outcome benefit of APRV in pediatric 
hypoxemic respiratory failure has not been proven.

High-Frequency Ventilation
Mechanical ventilation at supraphysiologic rates and low tidal 
volumes, known as high-frequency ventilation (HFV), improves gas
exchange in a selected group of patients who show no response to traditional ventilatory modalities. The mechanism of alveolar ventilation in HFV is very different from that in conventional ventilation, in that HFV is less dependent on VT and more dependent on asymmetric velocities and convective dispersion of inspired gas. Patients with severe persistent hypoxic failure are most likely to benefit from HFV. HFV is also helpful in patients with bronchopulmonary fistula and persistent air leaks. The main tenet of HFV is to recruit lung volume with a high MAP and produce smaller fluctuations in alveolar pressure during inspiration and expiration, thus maintaining a satisfactory FRC and reducing alveolar stretch. The 2 most investigated techniques of HFV are high-frequency oscillation (HFO) and high-frequency jet ventilation (HFJV).

The most commonly used HFV modality is HFO, which employs a mechanism to generate to-and-fro air movement. Additional air is dragged in (entrained) through a parallel circuit via a Venturi effect. Air is pushed in during inspiration and actively sucked out during expiration. The main determinants of oxygenation are Fio₂ and MAP, whereas ventilation is determined by changes in pressure (amplitude) from the MAP. Commonly used respiratory frequency varies from 5 Hz (300 breaths/min) in adults and older children, to 6-8 Hz (360-480 breaths/min) in young children, 8-10 Hz (480-600 breaths/min) in infants, and 10-12 Hz (600-720 breaths/min) in newborn and premature babies.

In HFJV, a high-frequency interrupter is interposed between a high-pressure gas source and a small cannula that is incorporated in the endotracheal tube (ET). The cannula propels tiny amounts of gas (jets) at high velocity and high frequency through the ET. An additional amount of gas is entrained from a parallel circuit. Unlike in HFO, expiration occurs passively in HFJV as a result of elastic recoil of the lung and the chest wall. PEEP is set through the parallel circuit by a mechanism to generate to-and-fro air movement. Additional air is dragged in (entrained) through a parallel circuit via a Venturi effect. Air is pushed in during inspiration and actively sucked out during expiration. The main determinants of oxygenation are Fio₂ and MAP, whereas ventilation is determined by changes in pressure (amplitude) from the MAP. Commonly used respiratory frequency varies from 5 Hz (300 breaths/min) in adults and older children, to 6-8 Hz (360-480 breaths/min) in young children, 8-10 Hz (480-600 breaths/min) in infants, and 10-12 Hz (600-720 breaths/min) in newborn and premature babies.

CONVENTIONAL VENTILATOR SETTINGS

**FiO₂**

The shape of the hemoglobin–oxygen dissociation curve dictates that oxygen content in the blood is not linearly related to PaO₂. A PaO₂ value that results in an oxyhemoglobin saturation of 95% is reasonable in most situations, because a higher PaO₂ would cause minimal increase in arterial oxygen content, and a modest (~10 torr) drop in PaO₂ would result in minimal decrease in oxyhemoglobin saturation. In most cases, a PaO₂ value of 70-75 torr is a reasonable goal. Fio₂ values that are higher than those necessary to attain oxyhemoglobin saturations of 95% expose the patient to unnecessary oxygen toxicity. Whenever possible, Fio₂ values should be decreased to a level ≤50.4 as long as oxyhemoglobin saturation remains 95% or above.

**Mode**

The choice of mode of ventilation depends on how much ventilator–patient interaction is desired and the disease entity that is being treated. SIMV or AC is chosen as the control mode, PCV, VCV, or PRVC is chosen as the variable that is to be controlled, and pressure support and volume support are the choices for support modes.

**Tidal Volume and Rate**

As previously discussed, alveolar ventilation, the chief determinant of PaCO₂, is calculated using VT, respiratory rate, and dead space volume. A change in VT results in a corresponding change in VA without affecting the dead space ventilation. A change in respiratory rate will affect the VA as well as the dead space ventilation. As mentioned earlier, the choice of VT and rate depends on the time constant. In a patient with relatively normal lungs, an age-appropriate ventilator rate and a VT of 7-10 mL/kg would be appropriate initial settings. Diseases associated with decreased time constants (decreased static compliance, e.g., ARDS, pneumonia, pulmonary edema) are best treated with small (6 mL/kg) VT and relatively rapid rates (25-40 breaths/min). Diseases associated with prolonged TCs (increased airway resistance, e.g., asthma, bronchiolitis) are best treated with relatively slow rates and higher (10-12 mL/kg) VT. In PCV, the delivered VT depends on the compliance and resistance of the patient’s respiratory system and needs to be monitored to ensure the appropriate amount for a given situation. An inflation pressure of 15-25 cm H₂O is sufficient for most patients, but it may need adjustment, depending on the amount of exhaled Vt observed. It should be emphasized that achieving a “normal” PaCO₂ value is not a goal of mechanical ventilation. Mild hypercapnia (permissive hypercapnia) should be acceptable, especially when one is attempting to limit injurious inflation pressures or Vr’s.

**Inspiratory Time and Expiratory Time**

Inspiratory time and expiratory time are adjusted by setting inspiratory flow rate in VCV and by setting the precise Ti in PCV. Increasing the inspiratory time results in an increase in MAP, improvement in oxygenation in diseases with decreased FRC, and better distribution of VT in obstructive lung disease. Sufficient expiratory time must be provided to ensure adequate emptying of the alveoli.

**Positive End-Expiratory Pressure**

The best level of PEEP depends on the disease entity that is being treated, and it may change in the same patient from time to time. Decisions are often based on the PaO₂/Fio₂ ratio and the measurement of dynamic compliance.

**PATIENT-VENTILATOR ASYNCHRONY**

Patient–ventilator asynchrony occurs when the patient’s respiratory pattern does not match that of the ventilator. This can occur during all phases of respiration. Adverse effects of patient–ventilator asynchrony include wasted effort, ineffective delivery of desired VT, excessive generation of in trathoracic pressure resulting in barotrauma and adverse effects on cardiac output, increased work of breathing, and patient discomfort. Although several mechanisms exist to facilitate patient–ventilator asynchrony, a certain amount of asynchrony is inevitable unless the patient is pharmacologically sedated and paralyzed.

**Triggering the Ventilator**

The patient must be able to trigger the ventilator without excessive effort. Ventilators can be pressure-triggered or flow-triggered. With pressure triggering, the inspiratory valve opens and flow is delivered when a set negative pressure is generated within the patient–ventilator circuit during both inspiration and expiration. The amount of pressure required to trigger an inspiration depends on the pressure trigger sensitivity. In flow triggering, the ventilator provides a base flow of gas through the ventilator–patient circuit. When a flow sensor on the expiratory limb of the patient–ventilator circuit detects a decrease in flow as a result of the patient’s inspiratory effort, the inspiratory valve opens and a ventilator breath is delivered. The degree of change in flow required to trigger an inspiration depends on the flow trigger sensitivity. Flow triggering is considered to be more comfortable, primarily because the patient receives some flow prior to triggering the ventilator, in contrast to pressure triggering, in which no flow is provided until the ventilator breath is triggered. Increasing the trigger sensitivity by decreasing the change in either pressure or flow needed to trigger an inspiration decreases the work of breathing. However, reducing the required pressure or flow excessively could result in accidental triggering and unwanted breaths by turbulence caused by condensation in the ventilator circuit, ET leaks, or cardiac oscillations.

**Selection of Appropriate Inspiratory Time**

The duration of Ti should match the patient’s own inspiratory phase. If Ti is too long, the patient's drive to exhale may begin before the ventilator breath has cycled off. When this occurs, exhalation occurs against inspiratory flow and a closed exhalation valve, resulting in increased work of breathing, excessive rise in intrathoracic pressure, and discomfort. If Ti is too short, the patient may be still inhaling when a ventilator breath has cycled off. This can cause patient–ventilator asynchrony, a certain amount of asynchrony is inevitable unless the patient is pharmacologically sedated and paralyzed.
individual patient observations and according to the type of lung disease present. In patients with severe lung disease (both obstructive and restrictive), unnatural Ti and Te values may have to be selected, as discussed earlier. In such situations, adequate analgesia, sedation, and, in extreme cases, neuromuscular blockade may be needed.

**Selection of Inspiratory Flow Pattern**

In VCV, inappropriate flow may be another source of patient–ventilator dyssynchrony. After initiation of inspiration, if the set amount of flow is inadequate to meet patient demand, a state of “flow starvation” occurs, resulting in excessive work of breathing and discomfort. Such cases may require a decelerating inspiratory flow pattern, in which a higher flow is provided in the beginning of inspiration and less toward the end as the lungs fill up. On the other hand, such a pattern may be uncomfortable for a patient who desires more gradual alveolar filling. The selection of inspiratory flow pattern should be based on the individual patient’s respiratory mechanics. In PCV and PSV, the inspiratory rise time determines the manner in which the airway pressure is raised and Vt delivered. Considerations for choosing the appropriate rise time in PCV and PSV are similar to those for choosing the inspiratory flow pattern in VCV.

**Use of Support Modes**

As much as possible, a conscious patient should be allowed to have spontaneous breaths that are supported by either PSV or VSV. This approach minimizes the mandatory breaths generated by the ventilator that are beyond the patient’s control to modulate. Therefore, continued assessments should be made to determine whether the patient is able to maintain ventilatory requirements more in support modes and less in control modes.

**Use of Sedation and Pharmacologic Paralysis**

Having a conscious but comfortable patient is a desirable goal during mechanical ventilation. Spontaneous breaths with good muscle tone and presence of cough are important for adequate clearance of tracheobronchial secretions. The patient’s ability to indicate distress is also important in identifying and preventing potential injurious factors. In certain situations, management of patient–ventilator asynchrony assumes far greater importance when the asynchrony is causing unacceptable derangement of gas exchange and ventilator-induced lung injury. Both alveolar interstitial lung pathology and obstructive airway diseases may necessitate unnatural and uncomfortable settings for respiratory rate, Ti, and inflation pressures. In such situations, deep sedation is often necessary. Benzodiazepines and opiates are the agents most commonly used for this purpose. In extreme situations, pharmacologic paralysis with a nondepolarizing agent, such as vecuronium, is required to abolish any patient effort and respiratory muscle tone. When pharmacologic paralysis is used, deep sedation must be ensured so that the patient does not sense pain and discomfort. Pharmacologic sedation and paralysis can ensure total control of the patient’s ventilation by mechanical means and may result in lifesaving improvement in gas exchange with reduction in inflation pressures. However, long-term use of such agents may be associated with undesirable consequences and higher morbidity. The risk of inadequate tracheobronchial secretions and atelectasis is potentially greater. Long-term use of pharmacologic sedation may be associated with chemical dependency and withdrawal manifestations, and prolonged neuromuscular blockade is associated with neuromyopathy in critically ill patients. The benefits of sedation and pharmacologic paralysis therefore should be carefully balanced with the risks, and periodic assessments should be made to determine the need for their continuation.

**Cardiopulmonary Interactions**

Mechanical ventilation can have both salutary as well as adverse effects on cardiac performance. By decreasing oxygen consumption necessary for work of breathing, oxygen supply to vital organs is improved. Positive-pressure breathing decreases left ventricular afterload, thus enhancing stroke volume and cardiac output in patients with failing myocardium (e.g., myocarditis). On the other hand, the decreased systemic venous return may further compromise stroke volume in hypovolemic patients. Such patients will require intravascular fluid loading. Also an increase in pulmonary vascular resistance (PVR) as a result of positive intrathoracic pressure may result in further uncompensation of a poorly performing right ventricle. PVR is at its lowest value at an optimum FRC. When FRC is too low or too high, PVR (and therefore the right ventricular afterload) is increased. Both desirable and undesirable effects of cardiopulmonary interactions may coexist and require ongoing assessment and necessary interventions.

**MONITORING RESPIRATORY MECHANICS**

**Exhaled Tidal Volume**

Exhaled tidal volume (Vte) is measured by a pneumotachometer in the ventilator circuit during exhalation. In VCV, part of the machine-delivered volume may leak out during inspiration and therefore never reach the patient. Measurement of Vte more accurately describes the Vt that is contributing to the patient’s alveolar ventilation. In PCV, the Vte depends on the patient’s respiratory system compliance and resistance, and therefore offers valuable diagnostic clues. A decrease in Vte during PCV is indicative of either decrease in compliance or increase in resistance and is helpful in directing the clinician to appropriate investigation and management. An increase in Vte is indicative of improvement and may require weaning of inflation pressures to adjust the Vte.

**Peak Inspiratory Pressure**

In VCV and PRVC, the PIP is the secondary variable determined by the patient’s respiratory system compliance and resistance. An increase in PIP in these modes is indicative of decreased compliance (e.g., atelectasis, pulmonary edema, pneumothorax) or increased resistance (e.g., bronchospasm, obstructed ET). During VCV and PRVC, decreasing the respiratory rate or prolonging the Ti will result in a lower PIP in patients with prolonged time constants because more time will be available for alveoli to fill. In such patients, a decrease in PIP suggests increased compliance or decreased resistance of the respiratory system.

**Respiratory System Dynamic Compliance and Static Compliance**

The changes in PIP during VCV and PRVC, and in Vte during PCV, are determined by Cdyn of the respiratory system (lung and chest wall). Dynamic compliance is calculated as follows:

\[ C_{dyn} = \frac{V_{te}}{(P_{PEEP} - P_{plat})} \]

It takes into account both the flow-resistive and the elastic properties of the respiratory system. Changes in Cdyn can be used to assess effects of different levels of PEEP as tidal ventilation is shifted along the slope of the volume-pressure curve (see Fig. 71-8). An increase in PEEP in alveolar-interstitial diseases (increased elastance), resulting in an increase in Cdyn suggests alveolar recruitment, whereas a decrease in Cdyn may indicate overdistention. Similarly, in obstructive diseases (increased resistance), adjustment in PEEP levels to ameliorate airway collapse during exhalation can be guided by monitoring Cdyn. To assess only the elastic recoil of the lung, measurement of Cstat when there is no airflow is required. This measurement is performed by using an inspiratory hold maneuver with the patient under neuromuscular blockade and observing pressure-time and flow-time waveforms (Fig. 71-11). During this maneuver, inspiratory flow ceases while the expiratory valve continues to remain closed, thus allowing pressure to equilibrate throughout the ventilator circuit and the patient’s lungs. This pressure, referred to as the plateau pressure (Pplat), is reflective of alveolar pressure. Cstat is calculated as follows:

\[ C_{stat} = \frac{V_{te}}{(P_{plat} - P_{PEEP})} \]

The difference between Cdyn and Cstat is attributable to airway resistance. This difference is minimal in alveolar-interstitial diseases but substantial in airway obstruction.
Evidence shows that in patients with severe acute hypoxemic respiratory failure, cytokines are released, exacerbating the injury and promoting fluid and protein transudation in the alveoli. Inflammatory mediators imbalance between alveolar epithelial and capillary endothelial cells, causing volutrauma and barotrauma. This volutrauma and barotrauma can lead to disruption of tight junctions in the lung, thereby delaying airway closure during exhalation and improving alveolar emptying.

Assessment of Auto-PEEP

Auto-PEEP is assessed with the use of an expiratory pause maneuver in which inspiration is delayed and alveolar pressure is allowed to equilibrate with the airway. In diseases with airway obstruction, insufficient alveolar emptying may occur if exhalation time is not adequate. The alveolar pressure in excess of the set PEEP at the completion of the expiratory pause is measured as auto-PEEP or intrinsic PEEP. Auto-PEEP can have adverse effects on ventilation and hemodynamic status. It can be managed by decreasing the respiratory rate or inspiratory time and thus allowing greater time for exhalation. Auto-PEEP may also be managed by increasing the set PEEP ("extrinsic" PEEP), thereby delaying airway closure during exhalation and improving alveolar emptying.

Assessment of Dead Space Ventilation

Positive pressure ventilation and application of PEEP may result in a decrease in venous return, cardiac output, and, therefore, also the pulmonary perfusion. Ventilation of poorly perfused alveoli results in dead space ventilation, which does not contribute to gas exchange. The dead space–VT fraction can be calculated with the following equation:

\[ \frac{V_d}{VT} = \left( \frac{P_{ACO_2} - P_{ECO_2}}{P_{ACO_2}} \right) + \frac{P_{ACO_2}}{P_{ACO_2}} \]

Normal \( \frac{V_d}{VT} \) is 0.33. Increased \( \frac{V_d}{VT} \) is indicative of poorly perfused alveoli. Patients with increased \( \frac{V_d}{VT} \) may require intravascular volume infusion or other means of augmenting the cardiac output to improve pulmonary perfusion. The \( \frac{V_d}{VT} \) fraction is calculated and displayed by commercially available capnographs, which measure endotracheal \( P_{CO_2} \) continuously.

**VENTILATOR-INDUCED LUNG INJURY**

Like most medical therapies, mechanical ventilation can be harmful if appropriate principles are not followed. Lung volumes that are too high or too low should be avoided. In attempting to recruit and maintain FRC, the clinician must be careful not to overdistend alveoli. Excessive PIP and VT can lead to unwelcome stress and strain on alveolar walls. This volutrauma and barotrauma can lead to disruption of tight junctions between alveolar epithelial and capillary endothelial cells, causing fluid and protein transudation in the alveoli. Inflammatory mediators and cytokines are released, exacerbating the injury and promoting exudative fluid formation. Decreased production and inactivation of surfactant result in atelectasis and further impairment of gas exchange. Evidence shows that in patients with severe acute hypoxemic respiratory failure, avoidance of VT \( \geq 10 \text{ mL/kg} \) and \( P_{PEEP} \geq 30 \text{ cm H}_2\text{O} \) limits diffuse alveolar damage.

Insufficient PEEP is another important mechanism of ventilator-induced lung injury. Alveoli that are recruited during inspiration must remain open during expiration; if they do not, atelectrauma occurs, which is defined as undesirable shear stress on alveolar walls as they are opened and closed repeatedly. Therefore, the ideal PEEP for a patient should maximize the number of open alveoli and minimize the number of overdistended alveoli. Careful adjustments of PEEP may also permit the clinician to wean a patient from a high inspired oxygen concentration, another potential source of lung injury (oxytrauma). Though most patients receive an inspired oxygen concentration of 100% during endotracheal intubation and at the beginning of mechanical ventilation, increasing PEEP to recruit alveoli without overdistention should be quickly instituted to improve oxygenation and permit weaning of the Fi\( O_2 \). Although an Fi\( O_2 \) value below which there is no risk of oxygen toxicity is unknown, most clinicians aim for a value <0.6.

**Ventilator-Associated Pneumonia**

The pathophysiology of ventilator-associated pneumonia (VAP) is multifactorial. Aspiration of oral and/or gastric secretions, colonization of ETs, and suppression of cough reflexes with sedation all play a role. New-onset fever and leukocytosis accompanied by demonstration of an infiltrative process by chest radiographs are consistent with a diagnosis of VAP. This complication can lead to worsened gas exchange, increased duration of ventilation, and even death. Elevation of the head of the bed to 30 degrees after initiation of mechanical ventilation and use of a protocol for oral decontamination during mechanical ventilation are two means of reducing the risk for VAP. The most effective strategy to minimize any of the aforementioned complications is regular assessment of extubation readiness and liberation from mechanical ventilation as soon as clinically possible.

**Weaning**

Weaning from mechanical ventilation should be considered as a patient's respiratory insufficiency begins to improve. Most pediatricians favor gradual weaning from ventilator support. With SIMV, the ventilator rate is slowly reduced, allowing the patient's spontaneous breaths (typically assisted with pressure or volume support) to assume a larger proportion of the minute ventilation. When the ventilator rate is low (<5 breaths/min) such that its contribution to minute ventilation is minimal, assessment of extubation readiness is performed. An alternative method of gradual weaning is transition to a pressure support mode of ventilation. In this mode, no ventilator rate is set, allowing all triggered breaths to be assisted with pressure support. The clinician reduces the pressure support slowly to a low value (<5–10 cm H\( O_2 \)), at which point assessment of extubation readiness is performed. During either technique, weaning should be halted if tachypnea, increased work of breathing, hypoxemia, hypercapnia, acidosis, diaphoresis, tachycardia, or hypotension occurs.

The most objective means of assessing extubation readiness is a spontaneous breathing trial (SBT). Prior to performance of an SBT, a patient should be awake with intact airway reflexes, capable of handling oropharyngeal secretions, and with stable hemodynamic status. In addition, gas exchange should be adequate, defined as a Pa\( O_2 \) >60 mm H\( g \) while receiving an Fi\( O_2 \) <0.4 and PEEP ≤5 cm H\( O_2 \). If these criteria are present, a patient should be started on CPAP with minimal or no pressure support (≤5 cm H\( O_2 \)). If this SBT is tolerated without episodes of respiratory or cardiovascular decompensation, successful extubation is likely. Some neonates and small children cannot be calmed or consoled long enough to complete the SBT. In this situation, extubation readiness must be assessed on a low level of ventilator support. Data suggest that there is a low risk of extubation failure if the patient’s respiratory physiology is within normal limits and has stable hemodynamic status with adequate gas exchange and spontaneous VT >6.5 mL/kg while receiving <20% of total minute ventilation from the ventilator. Certain patient populations are at increased risk for extubation failure, such as young infants, children mechanically ventilated for >7 days, and patients with chronic respiratory or neurologic conditions. These children often benefit from transition to a noninvasive form of positive pressure ventilation (e.g., high-flow nasal cannula, CPAP, or BiPAP).

![Figure 71-11 Alveolar pressure is best determined by measurement of plateau pressure (\( P_{plat} \)). Inspiration is paused for an extended period, and alveolar gas pressure is allowed to equilibrate with the ventilator circuit pressure. Airway pressure at the end of the inspiratory pause is \( P_{PEEP} \). The difference between peak inspiratory pressure (PIP) and \( P_{PEEP} \) is to overcome flow-resistive properties of the lung, whereas \( P_{PEEP} \) reflects the pressure needed to overcome elastic properties of lung and chest wall.](image-url)
delivered via nasal prongs or face mask to increase the odds of successful extubation. The likelihood of postextubation upper airway obstruction, the most common cause of extubation failure in children, cannot be predicted on the basis of an SBT result or bedside measurements of physiologic variables. Traumatic endotracheal intubation and subglottic swelling from the ET irritation, especially in patients who exhibit agitation while receiving mechanical ventilation, are common causes of airway narrowing after extubation. Administration of intravenous corticosteroids (dexamethasone 0.5 mg/kg every 6 hr for 4 doses prior to extubation) has been shown to minimize the incidence of postextubation airway obstruction. In patients in whom postextubation airway obstruction develops, the need for re-intubation may be obviated by administration of nebulized racemic epinephrine and heliox.

Bibliography is available at Expert Consult.

71.2 Long-Term Mechanical Ventilation

See Chapter 418.
**Bibliography**


Changes in 2011 Guidelines for Field Triage

Children Requiring Pediatric Trauma Center Care

Patients with serious injury to >1 organ or system
Patients with 1-system injury who require critical care or monitoring in an intensive care unit
Patients with signs of shock who require >1 transfusion
Patients with fracture complicated by suspected neurovascular or compartment injury
Patients with fracture of the axial skeleton
Patients with ≥2 long-bone fractures
Patients with potential replantation of an extremity
Patients with suspected or actual spinal cord or column injury
Patients with head injury with any 1 of the following: orbital or facial bone fracture, cerebrospinal fluid leak, altered state of consciousness, changing neurologic signs, open-head injury, depressed skull fracture, requiring intracranial pressure monitoring, patients suspected of requiring ventilator support.

To be done up to 3 hours after injury, when faced with multiple casualties and limited resources, the treatment may be decided in an organized manner that maximizes the potential for survival and the least potential for complications. In such cases, a rapid survey of the patient's injuries may help to determine whether the child requires critical care or monitoring. We recommend the following criteria to be used for triage of children in the field: (1) presence of shock, (2) presence of a significant injury that is time-sensitive, (3) presence of a major head injury, and (4) presence of a major musculoskeletal injury.

Table 72-2

<table>
<thead>
<tr>
<th>Table 72-2</th>
<th>Children Requiring Pediatric Trauma Center Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with serious injury to &gt;1 organ or system</td>
<td>Patients with 1-system injury who require critical care or monitoring in an intensive care unit</td>
</tr>
<tr>
<td>Patients with signs of shock who require &gt;1 transfusion</td>
<td>Patients with fracture complicated by suspected neurovascular or compartment injury</td>
</tr>
<tr>
<td>Patients with fracture of the axial skeleton</td>
<td>Patients with ≥2 long-bone fractures</td>
</tr>
<tr>
<td>Patients with potential replantation of an extremity</td>
<td>Patients with suspected or actual spinal cord or column injury</td>
</tr>
<tr>
<td>Patients with head injury with any 1 of the following: orbital or facial bone fracture, cerebrospinal fluid leak, altered state of consciousness, changing neurologic signs, open-head injury, depressed skull fracture, requiring intracranial pressure monitoring, patients suspected of requiring ventilator support.</td>
<td>Modified from Krug SE. The acutely ill or injured child. In Behrman RE, Kliegman RM, editors: Nelson essentials of pediatrics, ed 4, Philadelphia, 2002, WB Saunders, p. 96.</td>
</tr>
</tbody>
</table>
The Acutely Ill Child

Figure 72-1 Guidelines for Field Triage of Injured Patients—United States, 2011. (From Guidelines for Field Triage of Injured Patients: recommendations of the National Expert Panel on Field Triage. MMWR 61:6, 2012.)

Measure vital signs and level of consciousness

Step One

<table>
<thead>
<tr>
<th>Glasgow Coma Scale</th>
<th>≤13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>&lt;90 mmHg</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>≤10 or &gt;29 breaths per minute* (≤20 in infant aged &lt;1 year), or need for ventilatory support</td>
</tr>
</tbody>
</table>

Assess anatomy of injury

Step Two

| All penetrating injuries to head, neck, torso and extremities proximal to elbow or knee |
| Chest wall instability or deformity (e.g., flail chest) |
| Two or more proximal long bone fractures |
| Crushed, degloved, mangled, or pulseless extremity |
| Amputation proximal to wrist or ankle |
| Pelvic fractures |
| Open or depressed skull fracture |
| Paralysis |

Assess mechanism of injury and evidence of high-energy impact

Step Three

| Falls |
| Adults: ≥20 feet (one story is equal to 10 feet) |
| Children*: ≥10 feet or two or three times the height of the child |
| High-risk auto crash |
| Intrusion,** including roof: ≥12 inches occupant site; ≥18 inches any site |
| Ejection (partial or complete) from automobile |
| Death in same passenger compartment |
| Vehicle telemetry data consistent with a high risk of injury |
| Auto vs. pedestrian/bicyclist thrown, run over, or with significant (>20 mph) impact†† |
| Motorcycle crash ≥20 mph |

Assess special patient or system considerations

Step Four

| Older adults¶¶ |
| Risk of injury/death increases after age 55 years |
| SBP <110 might represent shock after age 65 years |
| Low impact mechanisms (e.g., ground level falls) might result in severe injury |
| Children |
| Should be triaged preferentially to pediatric capable trauma centers |
| Anticoagulants and bleeding disorders |
| Patients with head injury are at high risk for rapid deterioration |
| Burns |
| Without other trauma mechanism: triage to burn facility*** |
| With trauma mechanism: triage to trauma center*** |
| Pregnancy > 20 weeks |
| EMS provider judgment |

When in doubt, transport to a trauma center

 starred criteria in Step One or mechanism identified in Step Two triggers a “yes” response.

† Trauma centers are designated Level I-IV. A Level I center has the greatest amount of resources and personnel for care of the injured patient and provides regional leadership in education, research, and prevention programs. A Level II facility offers similar resources to a Level I facility, possibly differing only in continuous availability of certain subspecialties or frequent prevention, education, and research activities for Level I designation; Level II facilities are not required to be resident or fellow education centers. A level III center is capable of assessment, resuscitation, and emergency surgery, with severely injured patients being transferred to a Level I or II facility. A Level IV trauma center is capable of providing 24-hour physician coverage, resuscitation, and stabilization to injured patients before transfer to a facility that provides a higher level of trauma care.

¶ Any injury noted in Step Two or mechanism identified in Step Three triggers a “yes” response.

** Intrusion refers to interior compartment intrusion, as opposed to deformation which refers to exterior damage.

†† Includes pedestrians or bicyclists thrown or run over by a motor vehicle or those with estimated impact ≥20 mph with a motor vehicle.

¶¶ Local or regional protocols should be used to determine the most appropriate level of trauma center within the defined trauma system; need not be the highest-level trauma center.

¶¶ Age >55 years.

*** Patients with both burns and concomitant trauma for whom the burn injury poses the greatest risk for morbidity and mortality should be transferred to a burn center. If the nonburn trauma presents a greater immediate risk, the patient may be stabilized in a trauma center and then transferred to a burn center.

**** Patients who do not meet any of the triage criteria in Steps One through Four should be transported to the most appropriate medical facility as outlined in local EMS protocols.

* The upper limit of respiratory rate in infants is >29 breaths per minute to maintain a higher level of overtriage for infants.

††† Patients who do not meet any of the triage criteria in Steps One through Four should be transported to the most appropriate medical facility as outlined in local EMS protocols.
When the receiving ED is notified before the child’s arrival, the trauma team should also be mobilized in advance. Each member has defined tasks. A senior surgeon (surgical coordinator) or, sometimes initially, an emergency physician leads the team. Team compositions vary somewhat from hospital to hospital; Figure 72-2 shows the model used at Children’s National Medical Center (Washington, DC). Consultants, especially neurosurgeons and orthopedic surgeons, must be promptly available; the operating room staff should be alerted.

Physiologic status, anatomic locations, and/or mechanism of injury are used for field triage as well as to determine whether to activate the trauma team. More importance should be placed on physiologic compromise and less on mechanism of injury. Scoring scales such as the Abbreviated Injury Scale (AIS), Injury Severity Score (ISS), Pediatric Trauma Score (Table 72-3), and Revised Trauma Score use these parameters to predict patient outcome. The AIS and ISS are used together. First, the AIS is used to numerically score injuries—as 1 component and 1 severity within each of 6 ISS body regions: head/neck, face, thorax, abdomen, extremity, and external. The ISS is the sum of the squares of the highest 3 AIS region scores.

**PRIMARY SURVEY**

During the primary survey, the physician quickly assesses and treats any life-threatening injuries. The principal causes of death shortly after trauma are airway obstruction, respiratory insufficiency, shock from hemorrhage, and central nervous system injury. The primary survey addresses the ABCDEs: Airway, Breathing, Circulation, neurologic Deficit, and Exposure of the patient and control of the Environment.

**Airway/Cervical Spine**

Optimizing oxygenation and ventilation, while protecting the cervical spine from potential further injury is of paramount importance. Initially, cervical spine injury should be suspected in any child sustaining multiple, blunt trauma. Children are at risk for such injuries because of their relatively large heads, which augment flexion–extension forces, and weak neck muscles, which predispose them to ligament injuries. To prevent additional spinal injury, the current standard is to immobilize the cervical (and thoracic and lumbar) spine in neutral position with a stiff collar, head blocks, tape or cloth placed across the forehead, torso, and thighs to restrain the child, and a rigid backboard.

Airway obstruction manifests as snoring, gurgling, hoarseness, stridor, and/or diminished breath sounds (even with apparently good respiratory effort). Children are more likely than adults to have airway obstruction because of their smaller oral and nasal cavities, proportionately larger tongues and greater amounts of tonsillar and adenoidal tissue, higher and more anterior glottic openings, and narrower larynxes and tracheas. Obstruction is common in patients with severe head injuries, owing in part to decreased muscle tone, which allows the tongue to fall posteriorly and occlude the airway. With trauma, obstruction can also result from fractures of the mandible or facial bones, secretions such as blood or vomitus, crush injuries of the larynx or trachea, or foreign body aspiration.

If it is necessary to open the airway, a jaw thrust **without head tilt** is recommended. This procedure minimizes cervical spine motion. In an unconscious child, an oropharyngeal airway can be inserted to prevent posterior displacement of the mandibular tissues. A semiconscious child will gag with an oropharyngeal airway but may tolerate a nasopharyngeal airway. The primary survey includes a preliminary survey through a nasopharyngeal airway, followed by endotracheal intubation. End-expiratory carbon dioxide (CO2) detectors help verify accurate tube placement. If these maneuvers plus suctioning do not clear the airway, oral endotracheal intubation is indicated. When endotracheal intubation proves difficult, a laryngeal mask airway can be used as a temporary alternative. A laryngeal mask airway consists of a tube with an inflatable cuff that rests above the larynx and thus does not require placement of the tube into the trachea. Emergency cricothyrotomy is needed in <1% of trauma victims.

**Breathing**

The physician assesses breathing by counting the respiratory rate; visualizing chest wall motion for symmetry, expansion, and accessory muscle use; and auscultating breath sounds in both axillae. Continuous wave form capnography monitoring may also be used as an adjunct; however it is less reliable in patients with shock. In addition to looking visually for cyanosis, pulse oximetry is standard. If ventilation is inadequate, bag-valve-mask ventilation with 100% oxygen must be initiated immediately, followed by endotracheal intubation. End-expiratory carbon dioxide (CO2) detectors help verify accurate tube placement.

Head trauma is the most common cause of respiratory insufficiency. An unconscious child with a severe head injury may have a variety of breathing abnormalities, including Cheyne-Stokes respirations, slow irregular breaths, and apnea.

Although less common than a pulmonary contusion, tension pneumothorax and massive hemotorax are immediately life-threatening (Tables 72-4 and 72-5). **Tension pneumothorax** occurs when air accumulates under pressure in the pleural space. The adjacent lung is compressed, the mediastinum is pushed toward the opposite hemithorax, and the heart, great vessels, and contralateral lung are compressed or
Table 72-4  Life-Threatening Chest Injuries

<table>
<thead>
<tr>
<th>TENSION PNEUMOTHORAX</th>
<th>MASSIVE HEMORTHORAX</th>
<th>CARDIAC TAMPOANADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>One-way valve leak from the lung parenchyma or tracheobronchial tree</td>
<td>Ipsilaterally decreased more than contralaterally</td>
<td>Ipsilaterally decreased</td>
</tr>
<tr>
<td>Collapse with mediastinal and tracheal shift to the side opposite the leak</td>
<td>Ipsilaterally decreased</td>
<td>Normal</td>
</tr>
<tr>
<td>Compromises venous return and decreases ventilation of the other lung</td>
<td>Ipsilaterally decreased</td>
<td>Normal</td>
</tr>
<tr>
<td>Clinically, manifests as respiratory distress, unilateral absence of breath sounds, tracheal deviation, distended neck veins, tympany to percussion of the involved side, and cyanosis</td>
<td>Dull</td>
<td>Normal</td>
</tr>
<tr>
<td>Relieve first with needle aspiration, then with chest tube drainage</td>
<td>Midline</td>
<td>Midline</td>
</tr>
</tbody>
</table>

MAJOR FLAIL CHEST

Usually caused by blunt injury resulting in multiple rib fractures

Loss of bone stability of the thoracic cage

Major disruption of synchronous chest wall motion

Mechanical ventilation and positive end-expiratory pressure required

MASSIVE HEMOTHORAX

Must be drained with a large-bore tube

Initiate drainage only with concurrent vascular volume replacement

CARDIAC TAMPOANADE

Beck Triad:
1. Decreased or muffled heart sounds
2. Distended neck veins from increased venous pressure
3. Hypotension with pulsus paradoxus (decreased pulse pressure during inspiration)
   Must be drained

Effect on ventilation depends on size


Table 72-5  Differential Diagnosis of Immediately Life-Threatening Cardiopulmonary Injuries

<table>
<thead>
<tr>
<th>TENSION PNEUMOTHORAX</th>
<th>MASSIVE HEMORTHORAX</th>
<th>CARDIAC TAMPOANADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breath sounds</td>
<td>Ipsilaterally decreased more than contralaterally</td>
<td>Ipsilaterally decreased</td>
</tr>
<tr>
<td>Percussion note</td>
<td>Hyperresonant</td>
<td>Dull</td>
</tr>
<tr>
<td>Tracheal location</td>
<td>Contralaterally shifted</td>
<td>Midline or shifted</td>
</tr>
<tr>
<td>Neck veins</td>
<td>Distended</td>
<td>Flat</td>
</tr>
<tr>
<td>Heart tones</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Effect on ventilation depends on size


Table 72-6  Systemic Responses to Blood Loss in Pediatric Patients

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>MILD BLOOD LOSS (&lt;30%)</th>
<th>MODERATE BLOOD LOSS (30-45%)</th>
<th>SEVERE BLOOD LOSS (&gt;45%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Increased heart rate; weak, thready peripheral pulses; normal systolic blood pressure; normal pulse pressure</td>
<td>Markedly increased heart rate; weak, thready central pulses; peripheral pulses absent; low normal systolic blood pressure</td>
<td>Tachycardia followed by bradycardia; central pulses very weak or absent; peripheral pulses absent; hypotension; diastolic blood pressure may be undetectable</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Anxiety; irritability; confusion</td>
<td>Lethargy; dulled response to pain</td>
<td>Coma</td>
</tr>
<tr>
<td>Skin</td>
<td>Cool, mottled; capillary refill prolonged</td>
<td>Cyanotic; capillary refill markedly prolonged</td>
<td>Pale and cold</td>
</tr>
<tr>
<td>Urine output</td>
<td>Low to very low</td>
<td>Minimal</td>
<td>None</td>
</tr>
</tbody>
</table>

Adapted from American College of Surgeons Committee on Trauma: Advanced trauma life support for doctors: student course manual, Chicago, 2008, American College of Surgeons, p. 234.

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cutdown (e.g., in the saphenous vein). Ultrasonography can facilitate central venous catheter placement.

Aggressive, intravenous fluid resuscitation is essential early in shock to prevent further deterioration. Isotonic crystalloid solution, such as lactated Ringer injection or normal saline (20 mL/kg), should be infused rapidly. No consensus exists to support the routine use of colloid or hypertonic saline solution for shock (see Chapter 70). When necessary, repeated crystalloid boluses should be given. Most children are stabilized with administration of crystalloid solution alone. However, if the patient remains in shock after boluses totaling 40-60 mL/kg of crystalloid, then 10-15 mL/kg of cross-matched packed red blood cells should be transfused. Although less desirable, type-specific or O-negative cells can be substituted pending availability of cross-matched blood. When shock persists despite these measures, surgery to stop internal hemorrhage is usually indicated.

**Neurologic Deficit**

Neurologic status is briefly assessed by determining the level of consciousness and evaluating pupil size and reactivity. The level of consciousness can be classified using the mnemonic AVPU: Alert, responsive to Verbal commands, responsive to Painful stimuli, or Unresponsive.

Head injuries account for at least 75% of pediatric blunt trauma deaths. Primary direct cerebral injury occurs within seconds of the event and is irreversible. Secondary injury is caused by subsequent anoxia or ischemia. The goal is to minimize secondary injury by ensuring adequate oxygenation, ventilation, and perfusion, and maintaining normal intracranial pressure (ICP). A child with severe neurologic impairment—i.e., with a Glasgow Coma Scale (GCS; see Table 67-3 in Chapter 67) score of 8 or less—should be intubated. Signs of increased ICP, including progressive neurologic deterioration and evidence of transtentorial herniation, must be treated immediately (see Chapter 68). Hyperventilation lowers Paco₂, resulting in cerebral vasoconstriction, reduced cerebral blood flow, and decreased ICP. Brief hyperventilation remains an immediate option for patients with acute increases in ICP. Prophylactic hyperventilation or vigorous or prolonged hyperventilation is not recommended, because the consequent vasoconstriction may excessively decrease cerebral perfusion and oxygenation. Mannitol lowers ICP and may improve survival. Because mannitol acts via osmotic diuresis, it can exacerbate hypovolemia and must be used cautiously. Hypertonic saline may be a useful agent for control of increased ICP in patients with severe head injury and may possibly decrease mortality when compared with mannitol. Neurosurgical consultation is mandatory. If signs of increased ICP persist, the neurosurgeon must decide whether to operate emergently.

**Exposure and Environmental Control**

All clothing should be cut away to reveal any injuries. Cutting is quickest and minimizes unnecessary patient movement.

Children often arrive mildly hypothermic because of their higher body surface area : mass ratios. They can be warmed with use of radiant heat as well as heated blankets and intravenous fluids.

**SECONDARY SURVEY**

During the secondary survey, the physician completes a detailed, head-to-toe physical examination.

**Head Trauma**

A GCS or Pediatric GCS score (see Table 67-3 in Chapter 67) should be assigned to every child with significant head trauma. This scale assesses eye opening and motor and verbal responses. In the Pediatric GCS, the verbal score is modified for age. The GCS helps categorize neurologic disability, and serial measurements identify improvement or deterioration over time. Patients with low scores 6-24 hr after injuries have poor prognoses.

In the ED, CT scanning of the head without a contrast agent has become standard to determine the type of injury in patients with concerning findings. Diffuse cerebral injury with edema is a common and serious finding on CT scan in severely brain-injured children. Focal evacuable hemorrhagic lesions (e.g., epidural hematoma) occur less commonly but may require immediate neurosurgical intervention (Fig. 72-3).

Monitoring of ICP should be strongly considered for children with severe brain injury, particularly for those with a GCS score of 8 or less and abnormal head CT findings (see Chapter 68). An advantage of an intraventricular catheter over an intraparenchymal device is that cerebrospinal fluid can be drained to treat acute increases in ICP. Hypoxia, hypercarbia, hypotension, and hyperthermia must be aggressively managed to prevent secondary brain injury. Cerebral perfusion pressure should be maintained >40 mm Hg at least (although some experts recommend an even higher minimum).

A child with a severe brain injury must be treated aggressively in the ED because it is very difficult to accurately predict long-term neurologic outcome. Compared with adults with similar injuries, children are thought to have better functional outcomes.

**Cervical Spine Trauma**

Cervical spine injuries occur in <3% of children with blunt trauma—with the risk being substantially higher in those with GCS scores ≤8—but they are associated with significant mortality and morbidity. Bony injuries occur mainly from C1 to C4 in children younger than 8 yr. In older children, they occur equally in the upper and lower cervical spine. The mortality rate is significantly higher in patients with upper cervical spine injuries. Spinal cord injury without radiographic (vertebral body) abnormalities (SCIWORA) on plain films or CT may be present. Patients with SCIWORA have neurologic symptoms, and spinal cord abnormalities are nearly always noted on MRI. Approximately 30% of all patients with cervical spine injuries have permanent neurologic deficits.

Evaluation begins with a detailed history and neurologic examination. Identifying the mechanism of injury helps in estimating the likelihood of a cervical spine injury. Both the patient and the paramedic should be asked whether any neurologic symptoms or signs, such as weakness or abnormal sensation, were present before arrival in the...
ED. In a child with neurologic symptoms and normal findings on cervical spine plain radiographs and CT scan, SCIWORA must be considered.

Whenever the history, physical examination, or mechanism of injury suggests a cervical spine injury, radiographs should be obtained after initial resuscitation. The National Emergency X-Ray Utilization Study (NEXUS) cervical spine rule helps identify low-risk patients who may not require radiographs (Table 72-7). The standard series of plain radiographs includes lateral, anteroposterior, and odontoid views. Some centers use cervical spine CT as the primary diagnostic tool, particularly in patients with abnormal GCS scores and/or significant injury mechanisms, recognizing that CT is more sensitive in detecting bony injury than plain radiographs. CT is also helpful if an odontoid fracture is suspected, because young children typically do not cooperate enough to obtain an “open-mouth” (odontoid) radiographic view. Use of cervical spine CT scan must be balanced with the knowledge that CT exposes thyroid tissue to 90-200 times the amount of radiation from plain films. MRI is indicated in a child with suspected SCIWORA and may also be useful in the evaluation of children who remain obtunded.

Rapid diagnosis of spinal cord injury is essential. Initiating high-dose intravenous methylprednisolone within 8 hr of spinal cord injury has been shown to improve motor outcome and remains standard therapy.

**Thoracic Trauma**

Pulmonary contusions occur frequently in young children with blunt chest trauma. A child’s chest wall is relatively pliable; therefore, less force is absorbed by the rib cage, and more is transmitted to the lungs. Respiratory distress may be noted initially or may develop during the first 24 hr after injury.

Rib fractures result from significant external force. They are noted in patients with more severe injuries and are associated with a higher mortality rate. Flail chest, which is caused by multiple rib fractures, is rare in children. Indications for operative management in thoracic trauma are listed in Table 72-8. Table 72-5 shows the differential diagnosis of immediately life-threatening cardiopulmonary injuries.

**Abdominal Trauma**

Liver and spleen contusions, hematomas, and lacerations account for the majority of intra-abdominal injuries from blunt trauma. The kidneys, pancreas, and duodenum are relatively spared because of their retroperitoneal location. Pancreatic and duodenal injuries are more common after a bicycle handlebar impact or a direct blow to the abdomen (Table 72-9).

Although a thorough examination for intraabdominal injuries is essential, achieving it often proves difficult. Misleading findings can result from gastric distention after crying or in an uncooperative toddler. Calm reassurance, distraction, and gentle, persistent palpation help with the examination. Important findings include distention, bruises, and tenderness. Specific symptoms and signs give insight into the mechanism of injury and the potential for particular injuries. Pain in the left shoulder may signify splenic trauma. A lap belt mark across the abdomen suggests a bowel or mesenteric injury. The presence of certain other injuries, such as lumbar spinal fractures and femur fractures, increases the likelihood of intraabdominal injury.

An abdominal CT scan with intravenous contrast medium enhancement rapidly identifies structural and functional abnormalities and is the preferred study in a stable child. It has excellent sensitivity and specificity for splenic (Fig. 72-4), hepatic (Fig. 72-5), and renal injuries, but is not as sensitive for diaphragmatic, pancreatic, or intestinal injuries. Small amounts of free fluid or air or a mesenteric hematoma may be the only sign of an intestinal injury. Administration of an oral contrast agent is not routinely recommended for all abdominal CT scans, but it sometimes aids in identifying an intestinal, especially a duodenal, injury.

Although focused assessment with sonography in trauma (FAST) examination helps detect hemoperitoneum, the variably low sensitivity of this test in children suggests that it should not be used to exclude intraabdominal injury in patients with a high pretest probability for injury. Serial FAST exams over time may be used by skilled ultrasonographers to rule out injury in need of intervention. FAST is most useful in patients who have blunt trauma and are hemodynamically unstable or patients who require operative intervention for nondiagnostic injuries, because in these cases the performance of a CT scan may not be feasible.

Nonoperative treatment has become standard for hemodynamically stable children with splenic, hepatic, and renal injuries from blunt

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**Table 72-7** National Emergency X-Ray Utilization Study (NEXUS) to Rule Out Cervical Spine Injury Following Blunt Trauma

<table>
<thead>
<tr>
<th>Indication for Operation in Thoracic Trauma</th>
</tr>
</thead>
<tbody>
<tr>
<td>THORACOTOMY IMMEDIATELY OR SHORTLY AFTER INJURY</td>
</tr>
<tr>
<td>Massive continuing pneumothorax or large air leak from tracheobronchial injury (cannot expand lung and ventilate)</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
</tr>
<tr>
<td>Open pneumothorax</td>
</tr>
<tr>
<td>Esophageal injury</td>
</tr>
<tr>
<td>Aortic or other vascular injury</td>
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<tr>
<td>Acute rupture of the diaphragm</td>
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<tr>
<td>DELAYED THORACOTOMY</td>
</tr>
<tr>
<td>Chronic rupture of the diaphragm</td>
</tr>
<tr>
<td>Clotted hemotorax</td>
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<tr>
<td>Persistent chylothorax</td>
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<tr>
<td>Traumatic intracardiac defects</td>
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<tr>
<td>Evacuation of large foreign bodies</td>
</tr>
<tr>
<td>Chronic atelectasis from traumatic bronchial stenosis</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Table 72-8</th>
<th>Indications for Operation in Thoracic Trauma</th>
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</thead>
<tbody>
<tr>
<td>THORACOTOMY IMMEDIATELY OR SHORTLY AFTER INJURY</td>
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<tr>
<td>Massive continuing pneumothorax or large air leak from tracheobronchial injury (cannot expand lung and ventilate)</td>
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<td>Cardiac tamponade</td>
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<tr>
<td>Chronic atelectasis from traumatic bronchial stenosis</td>
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</tbody>
</table>


<table>
<thead>
<tr>
<th>Table 72-9</th>
<th>Frequency of Abdominal Organ Injury by Injury Mechanism</th>
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</thead>
<tbody>
<tr>
<td><strong>BLUNT</strong></td>
<td><strong>PENETRATING</strong></td>
</tr>
<tr>
<td>Organ</td>
<td>%</td>
</tr>
<tr>
<td>Spleen</td>
<td>30</td>
</tr>
<tr>
<td>Liver</td>
<td>28</td>
</tr>
<tr>
<td>Kidneys</td>
<td>28</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>14</td>
</tr>
<tr>
<td>Bladder/urethra/ureters</td>
<td>4</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3</td>
</tr>
<tr>
<td>Blood vessels</td>
<td>3</td>
</tr>
</tbody>
</table>

Pelvic Trauma

Pelvic fractures in children are much less common than in adults, occurring in approximately 4% of children with more severe blunt trauma. Pelvic fractures are typically caused by high forces (e.g., from high-speed motor vehicle crashes or pedestrian impacts) and are often associated with intraabdominal and/or vascular injuries. The pelvis itself forms a ring, and high-force impacts can lead to disruption of this ring. When the ring is disrupted in more than one location, such as the symphysis pubis and the sacroiliac joint, the ring can become unstable and displaced, potentially injuring large pelvic vessels and leading to massive blood loss. Catheter-directed embolization to control bleeding, performed by an interventional radiologist, may be required.

The pelvis should be assessed for stability by means of compression–distraction maneuvers. If instability is noted, immediate external fixation with a pelvis-stabilizing device or a sheet should be applied, and orthopedic consultation sought. A trauma patient with a potential pelvic fracture should receive an anteroposterior pelvic radiograph in the trauma bay, or a CT scan, if highly suspicious. Children without a high-risk clinical finding (i.e., GCS <14; abdominal pain or tenderness, pelvic tenderness, laceration, ecchymosis, or abrasion; positive urinalysis, or femur fracture) or a high-risk mechanism of injury (i.e., unrestrained motor vehicle collision, motor vehicle collision with ejection, motor vehicle collision rollover, auto vs. pedestrian, or auto vs. bicycle) are unlikely to have pelvic fractures, however.

Lower Genitourinary Trauma

The perineum should be inspected, and the stability of the bones of the pelvis assessed. Urethral injuries are more common in males. Findings suggestive of urethral injury include scrotal or labial ecchymoses, blood at the urethral meatus, gross hematuria, and a superiorly positioned prostate on rectal examination (in an adolescent male). Certain pelvic fractures also increase the risk for potential genitourinary injury. Any of these findings is a contraindication to urethral catheter insertion and warrants consultation with a urologist. Retrograde urethrocystogram and CT scan of the pelvis and abdomen are used to determine the extent of injury.

Extremity Trauma

Extremity fractures may initially be missed as clinicians attend to more life-threatening injuries. Thorough examination of the extremities is essential because extremity fractures are among the most frequently overlooked injuries in children with multiple trauma. All limbs should be inspected for deformity, swelling, and bruises; palpated for tenderness; and assessed for active and passive range of motion, sensory function, and perfusion.

Before radiographs are obtained, suspected fractures and dislocations should be immobilized, and an analgesic administered. Splinting a femur fracture helps alleviate pain and may decrease blood loss. An orthopedic surgeon should be consulted immediately to evaluate children with compartment syndrome, neurovascular compromise, open fracture, and most traumatic amputations.

Radiologic and Laboratory Evaluation

Some authorities recommend ordering multiple studies in the ED that include lateral cervical spine, anteroposterior chest, and anteroposterior pelvis radiographs; arterial blood gas analysis; serum lactate determinations; complete blood cell count; electrolyte measurements; blood glucose and blood urea nitrogen measurements; serum creatinine, amylase, and lipase determinations; liver function tests; prothrombin and partial thromboplastin time determinations; blood typing and cross-matching; and urinalysis. One benefit of standardizing the evaluation of patients with major trauma is that fewer decisions need to be made on an individual basis, possibly expediting ED management.

Some of these studies have prognostic importance. A large base deficit is associated with a higher mortality rate, and elevated lactate values correlate with poor prognosis.

There are limitations of standard tests. The lateral cervical spine radiograph can miss clinically significant injuries. Hemoglobin and hematocrit values provide baseline values in the ED, but they may not have yet equilibrated after a hemorrhage. Abnormal liver function test results or elevated serum amylase and lipase values may be noted in patients with significant abdominal trauma, but most patients with significant trauma to the abdomen already have clinical indications for CT scanning or surgery. The majority of previously healthy children have normal coagulation profiles; these may become abnormal after major head trauma. Although routine urinalysis or dipstick urine testing for blood has been recommended for children, other data suggest that this evaluation may be unnecessary in patients without gross hematuria, hypotension, or other associated abdominal injuries.
Clinical prediction rules that combine patient history with physical exam findings have been developed to identify those at low risk of injury for whom specific radiographic and laboratory studies may not be necessary. The NEXUS C-spine rule is a sensitive, easily applicable rule that was validated for adults and children, although the younger population was smaller (see Table 72-7). Several clinical prediction rules have been developed to identify children at low risk of traumatic brain injury (Table 72-10). Another clinical prediction rule has been developed to identify children at very low risk of clinically-important intra-abdominal injuries following blunt trauma (Table 72-11). Although this rule has a negative predictive value of 99.9%, it needs to be externally validated before widespread implementation.

Psychological and Social Support

Serious multisystem trauma may result in significant long-term psychological and social difficulties for the child and family, particularly when there is a major head injury. Like adults, children are at risk for depressive symptoms and posttraumatic stress disorder. Caregivers face persistent stress and have been noted to have more psychological symptoms. Psychological and social support, during the resuscitation period and afterwards, is extremely important. Parents often prefer to be offered the choice to be present during resuscitations. A member of the resuscitation team should be made responsible for answering the family’s questions and supporting them in the trauma room.

Bibliography is available at Expert Consult.
nonpharmacologic or additional pharmacologic methods of analgesia and anxiolysis are required for a young, frightened, or uncooperative child. The wound should be examined under proper light to enable identification of foreign bodies or damage to vessels, nerves, or tendons.

Many lacerations, especially heavily contaminated ones, benefit from irrigation, with either water or sterile saline, to reduce the risk of infection. It is important to recognize that many traumatic lacerations treated in the ED or office are only minimally contaminated, containing less than 10^2 bacterial colonies. In fact, in one of the few human studies on irrigation, irrigation did not decrease the infection rate of minimally contaminated scalp or facial lacerations in patients who presented to an ED within 6 hr of injury. Another concern is that higher-pressure irrigation may actually increase tissue damage, making the wound and adjacent tissue more susceptible to infection and delaying healing. These caveats notwithstanding, irrigation has benefits, although which technique to use—that is, which device, what size syringe, what size needle, which solution, how much volume, how much pressure—remains to be determined. These features may vary for different types of lacerations. In heavily contaminated wounds, the benefit of higher-pressure irrigation likely outweighs the harm of tissue damage. For heavily contaminated lacerations, a typical recommendation is to use a 35- to 65-mL syringe attached to a plastic splatter shield, or a 19-gauge needle if a splash shield is unavailable, and to irrigate with approximately 100 mL of solution per centimeter of wound. Conversely, for relatively clean wounds, lower-pressure irrigation minimizes tissue damage, which may be more important for outcome than any decrease in bacterial clearance that may ensue. Debridement of devitalized tissue with higher-pressure irrigation, scrubbing, or surgical excision can also be necessary in certain cases, such as crush injuries.

Most lacerations seen in the pediatric ED or office should be closed primarily. Contraindications to primary closure (e.g., certain bite wounds) do exist (see Chapter 724). Although it is commonly accepted that the time from injury to repair should be as brief as possible to minimize the risk of infection, there is no universally accepted guideline as to what length of time is too long for primary wound closure. Also, this length of time varies for different types of lacerations. A prudent recommendation is that higher-risk wounds should be closed within 6 hr at most after the injury but that some low-risk wounds (e.g., clean facial lacerations) may be closed as late as 12-24 hr.

Many lacerations can be closed with simple, interrupted, 4-0, 5-0, or 6-0, nonabsorbable sutures. For lacerations under tension, horizontal or vertical mattress sutures, which provide added strength and may evert the wound edges better, can be used instead. For lacerations in cosmetically significant areas, a running intradermal stitch may produce a less conspicuous, more aesthetic scar than simple or mattress skin sutures, which can leave unattractive track marks. Deeper lacerations may need repair with an absorbable dermal and/or fascial layer. Other complex lacerations, such as those involving the ear, eyelid, nose, lip, tongue, genitalia, or fingertip, sometimes require more advanced techniques as well as subspecialty consultation.

Staples, topical skin adhesives, and surgical tape are acceptable alternatives to sutures, depending on the laceration’s location and the healthcare provider’s preference. Staples are particularly useful for lacerations of the scalp, where the appearance of the scar tends to be less important. Topical skin adhesives (octylcyanoacrylates or butylcyanoacrylates) are ideal for linear, relatively superficial lacerations that have been tied around a part of the body and has rubbed against the skin. These injuries should alert the clinician to the likelihood of nonaccidental (including self-inflicted) trauma.

Treatment

All abrasions should be cleansed thoroughly, and any debris or foreign material removed. If debris is not removed, abnormal skin pigmentation, known as post-traumatic tattooing, can occur and can be difficult to treat. A nonadherent occlusive dressing or a topical antibiotic and conventional dressing should be applied. Tetanus prophylaxis should be administered, if indicated (see Chapter 211). Large and/or deep abrasions that have not healed in a few weeks require consultation with a plastic surgeon for more advanced care.

Bibliography is available at Expert Consult.
Bibliography

High-altitude illness represents a spectrum of clinical entities with neurologic and pulmonary manifestations that overlap in their presentations and share common elements of pathophysiology. Acute mountain sickness (AMS) is the relatively benign and self-limited presentation, whereas high-altitude pulmonary edema (HAPE) and high-altitude cerebral edema (HACE) represent the potentially
life-threatening manifestations. Children are at risk of developing these conditions as they travel to high mountainous locations with their families pursuing outdoor recreation, tourism, or relocation to high-altitude communities.

In 1987, it was estimated that more than 1 million visitors of all ages travelled annually to the remote high mountain ranges of Asia, Africa, and South America, and approximately 35 million visitors travelled annually to high-altitude recreation areas in the western United States; today these numbers are likely to be underestimations. Given the large number of families travelling to high-altitude mountain locations worldwide and the potential for 25% of those travelling to even moderate altitudes to develop altitude-related symptoms, this has become a significant public health issue. Significant morbidity among children travelling with their families to high altitude locations warrants improved education of the populations at risk and the clinicians who care for them.

**ETIOLOGY**

**Definitions**
The altitude threshold where clinical illness may begin to occur is 1,500 meters (~4,900 ft). At this altitude a mild impairment in oxygen transport begins, yet altitude illness is relatively rare until higher elevations are reached. Children with underlying medical problems that impair oxygen transport may be predisposed to developing altitude illness at these lower levels. At moderate high altitude, 2,500-3,500 meters (~8,000-11,500 feet) arterial oxygen saturation (SaO₂) is generally well maintained; however, mild tissue hypoxia may occur as a result of low arterial oxygen partial pressure (Pao₂) and altitude illness becomes common after rapid ascent over 2,500 m. This is the altitude range that most people visit and the elevation of many popular ski resorts in the United States, thus the most common range to find the greatest number of altitude illness cases. Very high altitude, 3,500-5,500 meters (~11,500-18,000 feet) is associated with the most serious altitude illness, as SaO₂ falls below 90%. Here saturations fall on the steep portion of the oxyhemoglobin dissociation curve, and marked desaturation may occur with relatively small increases in altitude. At these heights severe hypoxemia is seen with sleep, exercise and illness. HAPE and HACE are most common in this environment. *Extreme high altitude*, above 5,500 meters (~18,000 feet) generally results in severe altitude illness during acute ascent without supplemental oxygen. Acclimatization at intermediate altitudes is required to reach extreme altitudes. Complete acclimatization is not possible, and long visits in this range result in progressive deterioration.

**Environmental Considerations**
The partial pressure of oxygen (P<sub>O2</sub>) in the atmosphere decreases log-arithmically as geographic altitude rises, but oxygen remains a constant 20.93% of the barometric pressure. The degree of hypoxia is related to the geographic altitude and the local variability of barometric pressure. The shape of the earth is slightly flat at the poles and bulging at the equator. The atmospheric envelope that surrounds the earth has a similar shape; thus the barometric pressure and the relative altitude are lower at higher latitudes than at the equator. The atmospheric envelope also develops seasonal variations in its local thickness, resulting in barometric pressures that are lower and relative altitudes that are higher during the winter season. Local weather can also have a significant effect on barometric pressure from day to day. A strong low-pressure front can reduce the barometric pressure 10-20 mm Hg and result in a significant temporary increase (150-500 m) in relative altitude.

**GENERAL EFFECTS OF HYPOBARIC HYPOXIA**
Arterial oxygen saturation falls with increasing altitude, eventually triggering central chemoreceptor responses to produce hyperventilation in an attempt to normalize oxygen saturation; relative hypoventilation exacerbates the hypoxemia of high-altitude exposure. During sleep, periodic breathing associated with high-altitude exposure may result in periods of apnea, causing further arterial oxygen desaturation. Fluid homeostasis often shifts at altitude, resulting in a generalized fluid retention and redistribution into intracellular and interstitial spaces manifested by peripheral edema, decreased urinary output, and impaired gas exchange.

**Acclimatization**
Gradual ascents allowing for acclimatization over several weeks have allowed successful summiting of many of the world’s highest peaks without supplemental oxygen. Without this gradual approach, rapid exposure to extreme altitude results in loss of consciousness and asphyxia in a matter of minutes. Children may acclimatize at least as well if not better than adults when comparing heart rate and arterial saturation of children 7-9 yr of age to their parents during a slow ascent.

Some of the responses to hypoxia are mediated at the molecular level by hypoxia inducible factor (HIF). This transcriptional activator orchestrates the expression of hundreds of genes in response to both acute and chronic hypoxic conditions. Acclimatization begins at the altitude that causes the oxygen saturation of arterial blood to fall below sea level values. Most healthy, unacclimatized visitors to high altitude will not experience a significant drop in oxygen saturation (SaO₂ < 90%) until they reach elevations above 8,000 feet. Children with preexisting conditions that reduce oxygen transport may have altitude intolerance and hypoxic stress at lower levels. Of particular importance are both acute and chronic cardiac and respiratory illnesses. An individual’s inherent ability to acclimatize is also important. Some acclimatize easily without developing clinical symptoms, others may transiently develop AMS during acclimatization, and a few have marked reactions to altitude exposure, fail to acclimatize, and develop severe altitude illness. Previ-ous successful acclimatization may be predictive of future responses for adults in similar conditions but may not be the case for children.

The most important response to acute hypoxia is an increase in minute ventilation. Peripheral chemoreceptors in the carotid bodies respond to hypoxia by signaling the respiratory control center in the medulla to increase ventilation. This decreases alveolar carbon dioxide partial pressure resulting in a corresponding increase of alveolar oxygen tension and arterial oxygenation. This increased ventilation known as the hypoxic ventilatory response (HVR), varies in magni-tude among individuals, may be genetically predetermined, and is related to the ability to acclimatize. A low HVR and relative hypoventilation are implicated in the pathogenesis of both AMS and HAPE, whereas a strong HVR enhances acclimatization. As ventilation increases, a respiratory alkalosis occurs, exerting negative feedback on central respiratory control, limiting further ventilation increase. The kidneys excrete bicarbonate in an effort to compensate for the alkalosis. As the pH normalizes, ventilation rises slowly, reaching a maximum after 4-7 days. *This process is enhanced by acetazolamide, which induces a bicarbonate diuresis.*

Increased sympathetic activity and catecholamine release on ascent result in elevation of heart rate, blood pressure, cardiac output, and venous tone. Except at extreme altitudes, acclimatization results in the resting heart rate gradually returning to near sea level values. *Resting relative tachycardia is evidence of poor acclimatization.*

Hematopoietic acclimatization consists of an increase in hemoglo-bin and the number of red blood cells and increase in 2,3-diphosphoglycerate. After acute ascent, an early increase of up to 15% occurs in hemoglobin concentration primarily from fluid shifting into the extravascular space. Acclimatization leads to an increase in plasma volume and total blood volume. Erythropoietin is secreted in a HIF-mediated response to hypoxemia within hours of ascent, stimulating the production of new red blood cells, which begin to appear in the circulation in 4 or 5 days. Hypoxemia also increase 2,3-diphosphoglycerate, resulting in a rightward shift of the oxyhemoglobin dissociation curve, favoring release of oxygen from the blood to the tissues. This is counteracted by the leftward shift of the oxyhe-moglobin dissociation curve caused by the respiratory alkalosis from hyperventilation. The result is a net null change in the oxyhemoglobin curve and an increase in oxygen-hemoglobin binding in the lung, raising SaO₂. Climbers at extreme altitude respond with marked hyperventilation, alkalosis and leftward shift; this leftward shift favors oxygen loading in a hypoxic environment and increases SaO₂. Some
individuals with mutant hemoglobin and high oxygen-hemoglobin affinity have been found to acclimatize more efficiently at moderate altitudes than their normal counterparts.

**ACUTE MOUNTAIN SICKNESS**

**Epidemiology and Risk Factors**

The incidence of high-altitude illness depends on several variables including the rate of ascent, previous altitude exposure, and individual genetic susceptibility. Sleeping altitude, final altitude reached, and duration of stay at altitude are also clear risk factors for AMS development. AMS is very common with rapid ascent. Climbers around the world who ascend quickly (1 or 2 days) from sea level to altitudes of 14,000–20,000 feet have a very high incidence of AMS (27–83%). The rapid ascent profile associated with air travel to high altitude locations also results in high AMS attack rates. Trekkers who fly into the Khumbu region to explore the Mt. Everest area have a higher incidence of AMS (47%) compared with those who walk (23%). Skiers who visit resorts in the western United States from sea level generally fly or drive to the region but sleep at relatively moderate altitudes (6,300–9,700 ft). Among this population, AMS occurs in approximately 25%.

Children have the same incidence of AMS as adults. Individual (genetic) susceptibility for the development of AMS plays a significant role in risk assessment. Most individuals with previous histories of AMS after acute ascent are likely to experience similar symptoms with repeated visits to altitude. While anecdotal clinical experience supports this concept in children, limited data exist regarding recurrent AMS in children. Gender does not affect the incidence of AMS.

**Pathophysiology**

The symptoms of AMS develop several hours after arrival at high altitude, whereas the development of HAPE and HACE generally requires several days of altitude exposure. Because hypoxemia occurs within minutes of arrival, it cannot be the direct cause of high-altitude illness, but rather the initiating factor.

The clinical manifestations of AMS/HACE are primarily the result of central nervous system dysfunction caused by hemodynamic mechanical factors and biochemical mediators of permeability. The central nervous system (CNS) vasodilatory response to hypoxemia causes an increase in cerebral blood flow and volume. Significant elevation of brain volume is observed in moderate to severe AMS and HACE but has not been demonstrated in mild AMS. Hypoxic alteration of CNS vascular autoregulation and hypertension from exercise may increase pressure transmission to the brain's capillary beds resulting in transepidermal leakage and vasogenic edema. HIF-mediated vascular endothelial growth factor, the inducible form of nitric oxide synthase, reactive cytokines, and free radical formation may increase permeability. Both mechanical and biochemical activation of the trimeric vasogenic system have been proposed as the cause of high-altitude headache, the primary symptom of AMS. While vasogenic edema has been implicated in severe AMS and HACE, magnetic resonance imaging (MRI) reveals signal changes in subjects with and without clinical AMS.

Many of the responses to hypoxia and altitude exposure occur both in individuals who develop symptoms and those who remain free of AMS. To address the discrepancy in symptomatic illness, the “tight fit” hypothesis was proposed. This theory suggests that the development of AMS/HACE is the result of a lack of intracranial space to accommodate increasing volume from brain swelling and edema that develop at altitude. The adequacy of the intracranial and intraspinal space to buffer changes in brain and cerebrospinal fluid (CSF) volume is the central concept. Buffering occurs as the intracranial CSF is displaced via the foramen magnum into the space available in the spinal canal, followed by increased CSF absorption and decreased CSF production. Individuals with less CSF buffering capacity have less compliance and are hypothesized to become more symptomatic (develop AMS).

**Diagnosis**

In adults, the symptoms of mild AMS are similar to those of a viral syndrome, an ethanol “hangover,” or simple physical exhaustion. To diagnose AMS, an adult must be in the setting of a recent gain in altitude, be at the new altitude for at least several hours, and report a headache plus at least 1 of the following symptoms: gastrointestinal upset (anorexia, nausea, or vomiting), general weakness or fatigue, dizziness or lightheadedness, or difficulty sleeping. These symptoms comprise the adult Lake Louise criteria for AMS. The headache may vary from mild to severe; anorexia plus nausea, with or without vomiting, are common. Sleep disturbance caused by periodic breathing is common in all visitors to high altitudes but is exacerbated in the setting of AMS. All the symptoms of AMS can range in severity from mild to incapacitating. Symptoms develop within a few hours after ascent and generally reach maximum severity between 24 and 48 hr, followed by gradual resolution. Most adults become symptom free by the 3rd or 4th day. The vague nature of this presentation has resulted in many misdiagnoses and morbidity among adults. In the setting of recent altitude exposure, these symptoms warrant a presumptive diagnosis of AMS and limitation of further ascent. There are no diagnostic physical signs in cases of mild AMS. Any evidence of CNS dysfunction, such as mild ataxia or altered mentation, is early evidence of HACE. Similarly, while dyspnea on exertion is universal at high altitudes, dyspnea at rest is an early indicator of HAPE.

Among infants and older preverbal children (up to 3 yr of age), AMS is diagnosed using nonverbal criteria. In this age range, AMS is manifested by increased fussiness, decreased playfulness, decreased appetite, and sleep disturbance. In most cases of AMS in very young children, all of these symptoms are present. Fussiness is defined as a state of irritability that is not easily explained by a cause, such as tiredness, wet diaper, hunger, teething, or pain from an injury. Fussy behavior may include crying, restlessness or muscular tension. Decreased playfulness may be profound. Alterations of appetite may progress to frank vomiting. Sleep disturbance can manifest with either increased or decreased sleep when compared to normal patterns. Most often decreased sleep and the inability to nap are noted.

The diagnosis of AMS in older children with early language skills (ages 4–11 yr) may be made with cautious use of the adult Lake Louise criteria. The language used in this adult questionnaire may be too complex and may underestimate AMS if not understood by the child. This is particularly true for questions regarding headache (the key symptom of AMS) and gastrointestinal symptoms. An age-appropriate modified Lake Louise Score for 4–11 yr old children has been proposed and used in the research setting (Fig. 73-1). Evaluating for the presence of headache can be accomplished by asking if the “head hurts” or by using a visual “faces” pain scale. Gastrointestinal symptoms are evaluated by asking children if they are “hungry” rather than trying to evaluate their appetite.

Many of the symptoms manifested by AMS in children may also result from the disruption of normal routine with travel. A change in environment, sleeping accommodation, or eating options can result in a fussy child. The threshold scores for AMS diagnostic criteria are modified to account for these baseline variations. Parents can easily learn to recognize AMS in preverbal children using the Children’s Lake Louise Score to alert them to the constellation of alterations in fussiness (headache equivalent), appetite, playfulness and sleep in their young child (see Fig. 73-1). Educating parents to recognize the symptoms of AMS in themselves is also important as an ill parent can indirectly compromise a child’s safety.

Other acute illnesses can mimic AMS in young children. It must be emphasized that altered mental status, neurologic abnormalities, breathing difficulty or cyanosis are not part of uncomplicated AMS. Any of these signs warrant immediate medical attention. If serious bacterial illness, a surgical condition, or another problem meriting specific intervention is suspected in a child, descent to lower altitude is recommended to eliminate the confounding variable of altitude illness.

**Periodic Breathing**

Periodic breathing at altitude is common at all ages during sleep, resulting in brief repeated episodes of oxyhemoglobin desaturation. Prepubertal children (9–12 yr old) have similar night-time oxygen
Part IX ♦ The Acutely Ill Child

AMOUNT OF UNEXPLAINED FUSSINESS

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Fussiness</td>
<td>Intermittent Fussiness</td>
<td>Constant Fussiness</td>
<td>When Awake</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

INTENSITY OF FUSSINESS

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Fussiness</td>
<td>Moderate Fussiness</td>
<td>Severe Fussiness</td>
<td>When Awake</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FUSSINESS SCORE (FS) = Amount + Intensity

RATE HOW WELL YOUR CHILD HAS EATEN TODAY (E)

0—Normal
1—Slightly less than normal
2—Much less than normal
3—Vomiting or not eating

RATE HOW PLAYFUL YOUR CHILD IS TODAY (P)

0—Normal
1—Playing slightly less
2—Playing much less than normal
3—Not playing

RATE ABILITY OF YOUR CHILD TO SLEEP TODAY (S)

0—Normal
1—Slightly less or more than normal
2—Much less or more than normal
3—Not able to sleep

CLLS = FS + E + P + S

The CLLS must be ≥7 with both the FS ≥4 and E+P+S ≥3 to confirm acute mountain sickness.

Fussiness is defined as a state of irritability that is not easily explained by a cause, such as tiredness, hunger, teething or pain from an injury. Fussy behavior may include crying, restlessness, or muscular tension. Please rate your child's typical fussy behavior during the last 24 hr without the benefit of your intervention.

Management

The management of AMS must include strict adherence to the principle that further ascent to a higher sleeping altitude is contraindicated after the symptoms of altitude illness occur. Halting ascent or activity to allow further acclimatization may reverse the symptoms; however, the ascent exacerbates the underlying pathologic processes and may lead to disastrous results. Stopping further ascent and waiting for acclimatization treats most AMS in 1-4 days. Mild cases of AMS may be treated without descent if monitoring by a reliable caregiver is available. In addition to rest, symptomatic therapy includes analgesics and antiemetics. AMS that becomes worse or does not respond to maintenance of altitude, rest, and pharmacologic intervention mandates descent. Descent (500-1,000 m) is effective treatment for all forms of altitude illness and should be tailored to the individual response. The presence of neurologic abnormalities (ataxia or altered mentation) or evidence of pulmonary edema (dyspnea at rest) mandates descent because these signs indicate a progression of AMS to severe altitude illness.

Supplemental oxygen administration relieves AMS symptoms, including small amounts (1-2 L/min) given during sleep. In the wilderness, oxygen tanks are impractically heavy and are usually unavailable in adequate amounts; therefore, oxygen therapy is usually reserved for the more serious manifestations of high-altitude illness. In resort settings, oxygen may be readily available for use in the hotel or condominium, but use in children is often difficult. Hyperbaric therapy that simulates descent is also effective.

Treatment of headache and nausea can be beneficial during the course of mild AMS, and in many cases this may be all that is necessary. Ibuprofen and acetaminophen are useful for the treatment of high-altitude headache; evidence supports this conservative approach in children as well. For nausea and vomiting, ondansetron oral dissolving tablets may be used.

Acetazolamide is a carbonic anhydrase inhibitor that induces a renal bicarbonate diuresis, causing a metabolic acidosis that increases ventilation and arterial oxygenation. This respiratory stimulation improves sleep when the hypoxemia caused by periodic breathing is eradicated by acetazolamide. Acetazolamide accelerates acclimatization and, if
Table 73-1  Medications for Treatment of Altitude-Associated Illness in Children (No Studies in Children for High-Altitude Indications)

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>CLASSIFICATION</th>
<th>INDICATION</th>
<th>DOSE AND ROUTE</th>
<th>ADVERSE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide</td>
<td>Carbonic anhydrase inhibitor</td>
<td>AMS prevention*</td>
<td>2.5 mg/kg PO every 12 hours; maximum 125 mg/dose</td>
<td>Collateral effects include paresthesias and taste alteration</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Steroid</td>
<td>AMS prevention†</td>
<td>0.15 mg/kg PO/IM/IV every 6 hr; maximum 4 mg/dose</td>
<td>Risk of adverse effects precludes prophylactic use</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Calcium-channel blocker</td>
<td>HAPE treatment (small children)§</td>
<td>0.5 mg/kg PO every 4-8 hr; maximum 20 mg/dose</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Phosphodiesterase-5 inhibitor</td>
<td>HAPE§</td>
<td>0.5 mg/kg/dose PO every 4-8 hr; maximum 50 mg/dose every 8 hr</td>
<td>FDA warning against chronic use in children</td>
</tr>
</tbody>
</table>

*AMS prophylaxis is not routinely recommended in children. It is indicated when rapid ascent profile is unavoidable or previous altitude illness in child about to undergo similar ascent profile. Doses as low as 1.25 mg/kg every 12 hr have been successful in some children.
†Use not warranted due to risk of adverse effects. Use slow graded ascent or acetazolamide.
§Oxygen and descent are the treatment of choice for severe AMS. If acetazolamide is not tolerated dexamethasone may be used. Oxygen, descent, and dexamethasone should be used in HACE.
In emergency settings where oxygen and descent are not an option, then nifedipine is indicated.
In emergency settings where oxygen and descent are not an option, if nifedipine is not well tolerated, then sildenafil may provide an alternative.

_given early in the development of AMS, rapidly resolves symptoms. The dose for children is 2.5 mg/kg/dose given twice daily to a maximum of 250 mg/dose (Table 73-1). Treatment for 48 hr is usually adequate for resolution of symptoms.

The most common adverse reactions to acetazolamide in adults include paresthesia, polyuria, and taste alterations. Less common reactions include nausea, drowsiness, tinnitus, transient myopia, and, rarely, rash. Acetazolamide is a nonantibiotic sulfa compound that carries a low risk of cross-reactivity for individuals with an allergy to sulfa antibiotics. A history of anaphylaxis or severe skin reactions to any sulfa-containing medication contraindicates the use of acetazolamide. Acetazolamide should be avoided in breastfeeding mothers and pregnant women.

Dexamethasone is an effective alternative treatment for AMS in adults. Although dexamethasone can resolve the symptoms of AMS, it does not play a role in acclimatization and symptoms may recur when the treatment is withdrawn. Adverse reactions to dexamethasone of concern in the pediatric population are pancreatitis, pseudotumor cerebri, and interference with normal growth. While these reactions are generally seen with prolonged use, dexamethasone should be avoided in children for prophylaxis and used for treatment only in extreme situations where alternatives such as descent or oxygen therapy are unavailable. The dosage of dexamethasone is 0.15 mg/kg/dose orally every 6 hr to a maximum of 4 mg per dose.

**Prevention**

Individuals who have a known susceptibility to the development of AMS and those for whom slow ascent is impractical may consider prophylactic medication. *Acetazolamide remains the compound of choice for AMS prophylaxis.* Numerous studies have demonstrated its effectiveness in adults, and 125 mg twice daily starting 24 hr before ascent and continuing for the first 2 days at high altitude is recommended. The recommended dosage of acetazolamide for AMS prophylaxis for children is 2.5 mg/kg/dose orally up to 125 mg total given twice daily. Ibuprofen when compared to acetazolamide is equally efficacious in preventing headache in adults. Dexamethasone also prevents AMS. However the potential adverse effects in children preclude its use for prophylaxis in this age group. Recommendations for hydration are frequently given in the lay literature, yet no evidence supports this advice. Drinking excessive amounts of free water may lead to hyponatremia and possibly complicate altitude illness.

**HIGH ALTITUDE CEREBRAL EDEMA**

**Epidemiology and Risk Factors**

HACE is rare in children, but it is rapidly fatal if unrecognized. Generally seen in adults with prolonged stays above 3,000 m, HACE is usually associated with concurrent AMS or HAPE, but can occur on its own.

**Pathophysiology**

HACE is regarded as the extreme expression of the same pathophysiology underlying AMS. In patients with HACE, MRI studies reveal white matter changes consistent with vasogenic edema that correlate with symptoms; evidence of cytotoxic edema has also been described.

**Diagnosis**

HACE is differentiated from severe AMS by the presence of neurologic signs. Most common are ataxia and altered mental status including confusion, progressive decrease in responsiveness, and eventually coma. Less common are focal cranial nerve palsies, motor and sensory deficits, and seizures. CT imaging is consistent with edema and increased intracranial pressure. MRI shows a high T2 signal in the white matter, specifically in the splenium of the corpus callosum, with diffusion-weighted technique.

**Management**

Descent remains the most effective treatment for HACE. Supplemental oxygen, if available, is useful especially if descent is not possible or delayed. Portable hyperbaric treatment is beneficial but its use should not delay descent if feasible. Dexamethasone should be administered at a dose of 0.15 mg/kg per dose given orally every 6 hr. The few mild cases of HACE reported in children have recovered with dexamethasone and descent.

**HIGH ALTITUDE PULMONARY EDEMA**

**Epidemiology and Risk Factors**

HAPE is a noncardiogenic pulmonary edema characterized by extravasation of intravascular fluid into the extravascular space of the lung.
HAPE generally occurs in the setting of recent ascent, most often at altitudes above 2,500 m, but in some cases at altitudes as low as 1,740 m. Among children, HAPE occurs in 2 distinct settings. **Type I HAPE** (or simply HAPE) occurs in a child who resides at low altitude who travels to high altitude. **Type II HAPE** (also termed reentry HAPE or reascent HAPE) affects children who reside at high altitude but become ill on their return home after descent to lower altitudes. HAPE may also occur in children who develop acute respiratory illnesses that exacerbate hypoxia at high altitude. Fatal outcomes of HAPE in children have been reported. Most mild and moderate cases resolve without difficulty, however if unrecognized and untreated, rapid progression to death can occur, especially when infection or cardiac conditions complicate the illness.

The incidence of HAPE is highly variable, as it depends not only on the altitude attained, but also the speed of ascent and prior history of HAPE. HAPE is significantly less common than AMS and its incidence in children resident at low altitude appears to parallel that among low-altitude-resident adults. HAPE affects male and female children more equally than adults, among whom the observed male predominance appears due to strenuous sport activities and military assignments. The occurrence and even the pathophysiology of HAPE may vary by population and genetic background. Individuals of Tibetan ancestry, resident on the Himalayan plateau and having minimal admixture with other populations, represent the extreme of adaptation to high altitude and rarely experience HAPE. Other native populations residing at high altitude, such as Andeans, do not appear to be protected from HAPE, and certain populations may have genetic polymorphisms associated with pulmonary edema. A number of conditions may predispose a child to HAPE (Table 73-2). Preexisting viral respiratory infections have been linked to HAPE, especially in children. Cardiorespiratory conditions associated with pulmonary hypertension, such as atrial and ventricular septal defects, pulmonary vein stenosis, congenital absence of a pulmonary artery, and obstructive sleep apnea also predispose to HAPE. Down syndrome is also a risk factor for HAPE development, as are previously repaired congenital heart defects and the presence of hypoplastic lungs. Undiagnosed structural cardiopulmonary abnormalities may result in severe hypoxia and/or altitude illness once ascent occurs.

**Physiology**

Alveolar hypoxia results in vasoconstriction of pulmonary arterioles just proximal to the alveolar capillary bed. Hypoxic pulmonary vasoconstriction is a normal physiologic response to optimize ventilation/perfusion (V/Q) matching by redistributing regional pulmonary blood flow to areas of highest ventilation, thereby optimizing arterial oxygenation. Under conditions that result in widespread alveolar hypoxia, extensive pulmonary vasoconstriction will lead to significant elevations in pulmonary arterial pressure; uneven pulmonary vasoconstriction can result in localized overperfusion, increased capillary pressures, distention, and leakage in the remaining vessels. This explains the patchy and heterogeneous edema that is classically observed in HAPE. The combination of pulmonary hypertension and uneven pulmonary vasoconstriction appears to be necessary in the pathogenesis of HAPE. Children and adolescents acutely exposed to high-altitude hypoxia demonstrated pulmonary hypertension, with increases in pulmonary artery pressure inversely related to age. Once the vascular leak occurs and alveolar fluid accumulates, a defect in transepithelial sodium transport impairs the clearance of alveolar fluid and contributes to HAPE.

### Diagnosis

The diagnosis of HAPE is based on clinical findings and their evolution in the context of recent ascent from lower elevation. There is no single diagnostic test or constellation of laboratory findings. Symptoms commonly develop within 24–96 hr, and onset of symptoms often occurs during the first or second night at altitude when hypoxia may be exacerbated during sleep. HAPE generally is not observed beyond 5 days after ascent to altitude (unless additional ascent occurs) because pulmonary vascular remodeling and acclimatization have taken place. The minimum criteria to diagnose HAPE include: recent exposure to altitude, dyspnea at rest, radiographic evidence of alveolar infiltrates, and near-complete resolution of both clinical and radiographic signs within 48 hr after descent or institution of oxygen therapy. Portable ultrasound has been shown useful to diagnose HAPE through the finding of “comet tails,” artifacts created by microreflections of the ultrasound beam within interlobular septae thickened by interstitial and/or alveolar edema.

The symptoms of AMS and HAPE show considerable overlap, and AMS may precede the development of HAPE in approximately half of patients. Frequently patients first exhibit general malaise that may progress to more specific signs of dyspnea at rest, then cardiopulmonary distress. Young children may show agitation and general debility. Older children may complain of headache, and children of all ages frequently experience nausea and vomiting. Cough is a common pulmonary sign. Dyspnea at rest, orthopnea, cyanosis, tachycardia, and chest pain herald worsening compromise, which may advance within hours to production of pink-tinged sputum.

Findings on physical exam frequently are less severe than a patient’s chest radiograph and the hypoxemia on pulse oximetry would predict. Children often appear pale, with or without visible cyanosis. Low-grade fever (<38.5°C [101.3°F]) is common and respiratory rate is generally increased. Auscultation typically reveals rales, usually greater in the right lung than the left on presentation. The radiographic pattern of pulmonary edema can be highly variable, from patchy and peripherally to more homogeneous in severe cases (Fig. 73-2). Often, the right lung shows more radiographic changes of edema than the left. Cardio-megaly is an uncommon finding, but peribronchial and perivascular cuffing are frequent, as well as enlargement of the pulmonary artery.

<table>
<thead>
<tr>
<th>Table 73-2</th>
<th>Conditions Associated with Increased Risk of HAPE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Environmental</strong></td>
<td>Ascent above 2,500 m</td>
</tr>
<tr>
<td></td>
<td>Rapid rate of ascent (generally &gt;1,000 m per day)</td>
</tr>
<tr>
<td></td>
<td>Cold exposure</td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td>Anomalies causing increased pulmonary blood flow or increased pulmonary arterial pressure</td>
</tr>
<tr>
<td></td>
<td>Ventricular septal defect, atrial septal defect, patent foramen ovale, patent ductus arteriosus</td>
</tr>
<tr>
<td></td>
<td>Anomalous pulmonary venous return or pulmonary vein stenosis</td>
</tr>
<tr>
<td></td>
<td>Unilateral absent pulmonary artery or isolated pulmonary artery of ducal origin</td>
</tr>
<tr>
<td></td>
<td>Coarctation of the aorta</td>
</tr>
<tr>
<td></td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td><strong>Pulmonary</strong></td>
<td>Chronic lung disease</td>
</tr>
<tr>
<td></td>
<td>Bronchopulmonary dysplasia</td>
</tr>
<tr>
<td></td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td></td>
<td>Supplemental oxygen requirement at sea level</td>
</tr>
<tr>
<td></td>
<td>Perinatal respiratory distress</td>
</tr>
<tr>
<td></td>
<td>Persistent pulmonary hypertension of the newborn</td>
</tr>
<tr>
<td></td>
<td>Perinatal apnea or depression</td>
</tr>
<tr>
<td><strong>Sleep apnea</strong></td>
<td>Night cough</td>
</tr>
<tr>
<td><strong>Infectious</strong></td>
<td>Upper respiratory tract infection</td>
</tr>
<tr>
<td></td>
<td>Bronchitis/bronchiolitis</td>
</tr>
<tr>
<td></td>
<td>Pneumonitis</td>
</tr>
<tr>
<td></td>
<td>Otitis media</td>
</tr>
<tr>
<td><strong>Pharmacologic</strong></td>
<td>Any medication causing central nervous system and respiratory depression</td>
</tr>
<tr>
<td></td>
<td>Alcohol</td>
</tr>
<tr>
<td></td>
<td>Sympathomimetics</td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
<td>Down syndrome (trisomy 21)</td>
</tr>
<tr>
<td></td>
<td>History of premature birth or low birthweight</td>
</tr>
</tbody>
</table>
silhouette and dilation of more peripheral pulmonary arteries. Significant arterial oxygen desaturation, as measured by pulse oximetry, is a consistent finding, with saturations frequently below 75%. A complete blood count often reveals a leukocytosis with a left shift of the granulocyte series.

The differential diagnosis of HAPE includes pneumonia, bronchitis/bronchiolitis, asthma, and other forms of cardiogenic and noncardiogenic pulmonary edema as well as pulmonary embolism. HAPE is most frequently misdiagnosed as pneumonia or a viral respiratory illness, especially when suspicion of altitude-associated pathology is not appropriately high. The presenting signs of cough, dyspnea, and orthopnea, follow by sputum production can easily be misinterpreted as pneumonia, an impression that is reinforced by the frequent accompaniment of low-grade fever. Respiratory viral infections increase the risk of developing HAPE, which may lead to further confusion in diagnosis.

Complications of HAPE in children often relate to underlying, sometimes undiagnosed, cardiopulmonary pathology or coexisting viral infections which potentiate the severity of pulmonary edema and pulmonary hypertension. Acute altitude exposure in such circumstances may lead to severe presentations that progress rapidly to extreme hypoxemia or cardiac failure and death. Children with trisomy 21, with or without structural cardiac anomalies, show increased susceptibility to HAPE and rapid symptom progression. Neonatal respiratory distress with pulmonary hypertension has been linked to exaggerated hypoxic pulmonary vasoreactivity in early adulthood and thereby a theoretical predisposition to HAPE. Other conditions related to pulmonary overcirculation (atrial and ventricular septal defects, patent foramen ovale, patent ductus arteriosus) small cross-sectional area of the pulmonary vascular bed (unilateral absent pulmonary artery, pulmonary hypoplasia), obstruction to pulmonary venous return (total anomalous pulmonary venous return, pulmonary vein stenosis), or left-sided obstruction (coarctation of the aorta) potentiate HAPE. Inflammatory processes, such as viral infection, predispose to HAPE and may worsen hypoxemia. Infection with respiratory syncytial virus, in particular, may trigger severe pulmonary hypertension.

**Management**

Descent with supplemental oxygen is the treatment of choice for HAPE in children. When feasible, or in the absence of medical care, rapid descent of at least 500-1,000 m usually results in rapid recovery. As with all altitude illness the magnitude of the descent is tailored to the resolution of symptoms. Oxygen and bed rest without descent can be safe and effective treatment for mild HAPE in children where careful medical observation is available. Mild HAPE in children and young adults at 3,750 m has been treated with bed rest alone, although clinical recovery may be slower compared to treatment with supplemental oxygen.

Supplemental oxygen at altitude is administered at 2-6 L/min by nasal cannula for 48-72 hr to maintain an arterial oxygen saturation of at least 90%. Increasing oxygen saturation above 90% does not result in further reduction in pulmonary artery pressure and does not accelerate edema resolution in adults. Oxygen flow can be weaned with improvement in symptoms and saturations; at flow rates below 2-4 L/min, children may be sufficiently stable and comfortable to continue treatment at home under the monitoring of family. Instructions to avoid physical exertion and exposure to cold should be given to reduce exposure to factors known to elevate pulmonary artery pressure. Most children experience complete resolution of mild HAPE within 24-72 hr of oxygen therapy when treated at altitude of symptom onset.

Pharmacotherapy for pediatric HAPE is rarely needed since oxygen and descent are so effective. In emergency situations without the options of supplemental oxygen or descent, pharmacotherapy is indicated. Nifedipine has been well studied for the treatment of adult HAPE. Extrapolated dosing for children is 0.5 mg/kg/dose given orally every 4-8 hr and titrated to response (maximum 10 mg/dose). Liquid-filled capsules of nifedipine (10 mg/0.34 mL) can be punctured to obtain doses for children less than 20 kg; sustained-release formulations cannot be broken to obtain reliable smaller doses. Patients should be monitored for hypotension during nifedipine administration. Phosphodiesterase type 5 inhibitors have been studied for HAPE prevention in adults. Although sildenafil and tadalafil have shown effectiveness in adults, there is concern around use of this class of agents in young children after the U.S. Food and Drug Administration warning against the use of sildenafil for pediatric pulmonary hypertension.

Figure 73-2 AMS and HAPE. A healthy 15 yr old male flew from Buffalo, NY, to Denver, CO, and immediately drove with his school group from the airport to a ski resort at 9,300 feet in the Rocky Mountains. The following day he felt dizzy and complained of headache. Symptoms of headache and dizziness continued along with emesis daily for 2 days. A snowboarding coach brought the patient to the local emergency facility the next day because of dyspnea, cough, headache, emesis, and fatigue. Pulse oximetry showed an arterial saturation of 51%. Chest x-ray showed diffuse pulmonary edema (A). The patient was transported to Denver (5,280 feet) by ambulance with 15 L/min oxygen via a nonrebreathing mask. Saturations improved with descent and were 94% on arrival at the Children’s Hospital Colorado emergency department. Breath sounds remained coarse and the patient was tachycardic and tachypneic. Oxygen flow was weaned to 1 L/min shortly after admission. Two days after presentation, lung exam was improved, without crackles. Repeat chest x-ray showed clearing of edema pattern (B). The patient maintained adequate saturations without supplemental oxygen and was discharged. (Courtesy of the Department of Radiology, Children’s Hospital of Colorado.)
between 1 and 17 yr of age because of an apparent increase in mortality during long-term therapy. Alveolar fluid clearance is upregulated by β-adrenergic agonists and inhaled β-agonists may successfully prevent and treat HAPE.

**SPECIAL CONSIDERATIONS**

**Reentry HAPE**

Children residing at high altitude may also experience HAPE of the type termed reentry or reascent HAPE. Reentry HAPE occurs upon reascent to the altitude of residence after a sojourn to low altitude. Although stays at low altitude as short as 24 hr may be sufficient to trigger reentry HAPE, most cases occur after several days at lower altitude. Children between 4 and 18 yr of age are much more likely to develop reentry HAPE than adults.

Reentry HAPE has a significant probability of recurrence and may justify pharmacologic prophylaxis to prevent the accumulated burden of morbidity. Acetazolamide has been used empirically based on its blunting of hypoxic pulmonary vasoconstriction in adults and the potential risk of hypotension and reflex tachycardia with nifedipine. The β₁-adrenergic agonist salmeterol has also been shown effective as prophylaxis in adults. Nifedipine may be a reasonable prophylactic option in older children and adolescents with histories of multiple episodes of HAPE.

**Symptomatic High-Altitude Pulmonary Hypertension**

Infants and young children resident at high altitude may also experience symptomatic high-altitude pulmonary hypertension, also termed subacute infantile mountain sickness. All infants, regardless of altitude of gestation and birth have thickened and muscularized interlobular and intralobular pulmonary arteries and pulmonary artery pressure that are initially near systemic. While muscular regression and fall in pulmonary artery pressure occur rapidly at sea level, infants permanently residing at high altitude demonstrate slowed regression of these characteristics through infancy and even childhood. Certain infants become symptomatic with exaggerated hypoxemia and signs of subacute pulmonary hypertension; these signs correlate with pathologic findings of right ventricular hypertrophy and dilation, increased muscularization of the pulmonary arterial bed and eventual right-sided congestive heart failure. Treatment may require relocation to a lower altitude.

**Travel With Young Infants**

Newborn infants retain some of the circulatory characteristics of recent fetal life, and these can pose a unique risk for altitude exposure. The fetal circulation has high pulmonary resistance, low pulmonary blood flow and both intra- and extra-cardiac shunts that optimize oxygenation via the placenta instead of the fetal lungs. After birth, a transition begins that closes fetal shunts and establishes normal pulmonary circulation and oxygen transport. Exposure to marked hypoxia can result in reversion to fetal shunting patterns despite the absence of a placenta. Normal infants at sea level complete these changes in 4-6 wk, though for infants born at moderate or high altitude, changes may last 3 mo or longer. Travel to high altitude with young infants is generally safe after 4-6 wk when circulatory changes have occurred, breastfeeding is established, and congenital abnormalities may have been detected.

Air travel with young infants frequently raises questions about the effects of exposure to hypobaric hypoxia, as the pressurization of aircraft cabins may vary up to an altitude equivalent of 8,500 feet (approximately 2,600 m). Transoceanic flights are generally not long enough to trigger AMS or HAE; infants may experience transient desaturation with feedings during flight and likely experience discomfort because of dry air, and stress caused by noise and vibration. Former preterm infants without chronic lung disease who have attained 3 mo corrected gestational age do not appear to experience greater hypoxemia during air travel than term infants; infants with more significant lung disease merit hypoxic challenge or provision for supplemental oxygen in flight.

**Sickle Trait/Disease**

Children with sickle cell disease or sickle trait should avoid travel to altitude, as hypoxemia may trigger sickling and painful crises, including splenic crises. Up to 20% of pediatric patients with sickle cell and sickle-thalassemia disease may experience a vasocclusive crisis at moderate altitude or in pressurized aircraft. Oxygen is advised for air travelers with known sickle cell disease. Although the majority of children with sickle trait remain asymptomatic, children can experience splenic ischemia or infarction, with severe left upper quadrant pain. Splenic infarction may be more common in nonblack patients (often of Mediterranean origin) with sickle trait.

**PREVENTION**

A comprehensive approach to travel to high altitude with children should focus on 3 phases: planning the ascent and assessment of risk, recognition and management of altitude-associated illness, and follow-up of any illness relative to future travel or diagnostic testing necessary.

Planning for travel to high altitude with children should consider rate of ascent, formulation of an emergency plan for communication and evacuation, and availability of medical care at the high-altitude destination. Slow ascent with time for acclimatization is the best prevention for all forms of altitude illness. Ideally, the first night should be spent at an altitude no higher than 2,800 m and then 2-3 nights should be spent at 2,500-3,000 m, with a subsequent increase (to a new sleeping altitude) of not more than 500 m each night. One extra night of acclimatization (at the same sleeping altitude) should be taken for every 1,000 m gained. Rapid ascent by air may be avoidable through alternate routes or alternate means of transportation. Difficult descent situations (where further ascent may be necessary before descent is possible) should be avoided with children. The availability of medical care and evacuation from altitude will influence the degree of personal preparation necessary. Widespread coverage by cellular and satellite phone service may give a false sense of security in remote regions where both terrain and weather can limit the arrival of definitive help.

Medical risk assessment encompasses consideration of age, previous altitude-associated illness, and possible predisposing circumstances to altitude illness. Very young infants (younger than 4-6 wk) may not have completed the postnatal circulatory transition and may be more vulnerable to altitude-associated desaturation with periodic breathing, right-to-left shunting across the foramen ovale, and hypoxic pulmonary vasoconstriction. Infants who required supplemental oxygen during the neonatal period, especially for pulmonary hypertension, may be at risk for hypoxemia with prolonged altitude exposure. History and physical exam are useful to identify conditions predisposing to HAPE, including recent viral infections, cardiac malformations, or obstructive sleep apnea. Low-risk children should not need medications for prophylaxis and should use gradual ascent to prevent illness.

Prompt recognition of altitude-associated illness requires awareness of the context in which illness occurs and familiarity with the signs and symptoms. Parents are generally adept at recognizing deviation from baseline behavior of their children. Clinicians should emphasize to parents that breathing difficulty, cyanosis, cough productive of pink-tinged sputum, altered mental status, or neurologic abnormalities are not part of uncomplicated AMS, but instead are serious signs of potential HAPE or HACE that deserve immediate medical attention.

Descent is the mainstay of therapy for all forms of altitude-associated illness in children. When descent is not feasible or illness is mild, other therapeutic options may be chosen. Severe altitude illness or death can be avoided in children by adherence to 3 general principles:

1. Recognition of the early signs of altitude illness and willingness by adult caregivers to acknowledge them.
2. No further ascent, especially to sleep at a higher altitude, when experiencing even minor symptoms/signs of altitude illness.
3. Immediate descent if signs/symptoms worsen while resting/receiving treatment at the altitude of onset.

Uncomplicated AMS with full resolution of symptoms upon descent or treatment does not require diagnostic work-up, but may prompt discussion of slower ascent, specific plans for treatment, or even
prophylaxis for future travel. Signs of HAPE or severe hypoxemia in a child disproportionate to the altitude reached should prompt further diagnostic evaluation, including consideration of echocardiography. Underlying cardiac conditions may not be apparent on physical examination at low altitude; cardiac echocardiography or catheterization under conditions of controlled hypoxia or hypoxic exercise may be necessary. Families of HAPE-susceptible children should be advised to avoid travel during or shortly after viral infection.

Bibliography is available at Expert Consult.
Chapter 73  ◆  Altitude-Associated Illness in Children (Acute Mountain Sickness)


Drowning is one of the leading causes of childhood morbidity and mortality in the world. Prevention is the most important step to reducing the impact of drowning injury, followed by early initiation of cardiopulmonary resuscitation (CPR) at the scene.

**ETIOLOGY**

Children are at risk of drowning when they are exposed to a water hazard in their environment. The World Congress of Drowning definition of drowning is: “Drowning is the process of experiencing respiratory impairment from submersion/immersion in liquid.” The term drowning does not imply the final outcome—death or survival; the outcome should be denoted as fatal or nonfatal drowning. Use of this terminology should improve consistency in reporting and research; the use of confusing descriptive terms such as “near,” “wet,” “dry,” “secondary,” “silent,” “passive,” and “active” should be abandoned. The injury following a drowning event is hypoxia.

**EPIDEMIOLOGY**

From 2005-2009, an average of 3,880 people per year were victims of fatal drowning and an estimated 5,789 persons were treated in U.S. hospital emergency departments (EDs) for nonfatal drowning. Compared with other types of injuries, drowning has one of the highest case fatality rates. Highest drowning death rates were seen in children ages 1-4 yr and 15-19 yr (2.55 and 1.29/100,000, respectively). In children, drowning is second only to motor vehicle injury as a leading cause of death from unintentional injury in the United States. Pediatric hospitalization rates associated with drowning ranged from 4.7 to 2.4 per 100,000 between 1993 and 2008. Rates of fatal drowning hospitalization declined from 0.5 to 0.3 deaths per 100,000 during the same period. Morbidity following nonfatal drowning is poorly studied.

The risk of drowning and the circumstances leading to it vary by age (Fig. 74-1). Drowning risk also relates to other host factors including male gender, alcohol use, a history of seizures, swimming lessons. Environmental risk factors include exposure to water and varying supervision. These factors are embedded in the context of geography, climate, socioeconomic status, and culture.

**Children Younger Than 1 Year of Age**

Most (71%) drowning deaths in children younger than 1 yr occur in the bathtub, when an infant is left alone or with an older sibling. Infant tub seats or rings may exacerbate the risk by giving caregivers a false sense of security that the child is safe in the tub. The next major risk to this age group is the large (5-gallon) household bucket, implicated in 16% of infant drowning deaths. These buckets are approximately 30 cm tall and designed to not tip over when half full. The average 9-mo-old child tends to be top-heavy, so can easily fall head first into a half-full bucket, become stuck, and drown within minutes.

**Children 1-4 Years of Age**

Drowning rates are consistently highest in 1-4 yr old children, likely because of their curious, but unaware, nature, coupled with the rapid progression of their physical capabilities. U.S. rates are highest in the southern regions; in some areas as high as 7.62/100,000, which approaches rates seen in developing countries. A common factor in many of these deaths is a lapse in adult supervision, often <5 min. Most U.S. drownings occur in residential swimming pools. Usually, the child is in the child’s own home and the caregiver does not expect the child to be anywhere near the pool.

In rural areas, children in this age group often drown in irrigation ditches or nearby ponds and rivers. The circumstances are similar to those noted previously, in a body of water that is near the house. Drowning is one of the leading causes of farm injury–related deaths in children.

**School-age Children**

School-age children are at increased risk of drowning in natural bodies of water such as lakes, ponds, rivers, and canals. Although swimming pools account for the majority of nonfatal drownings, open water accounts for a higher death rate from this age group on through adolescence. Unlike for preschool children, swimming or boating activities are important factors in drowning injuries in school-aged children.

**Adolescents**

The second major peak in drowning death rates occurs in older adolescents, age 15-19 yr. Almost 70% drown in natural freshwater. In this age group particularly, striking disparities in drowning deaths exist in gender and race. Males account for 80% of fatal drownings. The drowning rates for adolescent males are nearly 10 times higher than those for adolescent females. The gender disparity may likely be related to males’ greater risk-taking behavior, greater alcohol use, less perception about risks associated with drowning, as well as greater belief in their swimming ability than females. In 2009, as in previous years, drowning rates for black males age 15-19 yr were nearly double those for white males of the same age. Racial differences are only partially explained by socioeconomic status; other cultural factors contribute. Black children are more likely to drown in unguarded public or apartment pools, whereas white children are more likely to drown in private residential pools. Hispanic and foreign-born children have lower rates of drowning than their white counterparts. Differences in exposure to swimming lessons, cultural attitudes, and fears about swimming, as well as experience around water, may contribute to drowning risk.

**Underlying Conditions**

Several underlying medical conditions are associated with drowning at all ages. A number of studies have found an increased risk, up to 19-fold, in individuals with epilepsy. Drowning risk for children with seizures is greatest in bathtubs and swimming pools. Cardiac etiologies, including arrhythmias, myocarditis, and prolonged QT syndromes have been found in some children who die suddenly in the water (see Chapters 435.5), particularly in those with a family history of syncope, cardiac arrest, prior drowning, or QT prolongation. Some children with long QT syndrome are misdiagnosed as having seizures.

Drowning may also be an intentional injury. A history of the event that changes or is inconsistent with the child’s developmental stage is the key to recognition of intentional drowning. Physical examination and other physical injuries rarely provide clues. Child abuse is more often recognized in bathtub-related drownings. Suicide usually occurs in lone swimmers in open water.

**Alcohol Use**

The use of alcohol and drugs greatly increases the risk of drowning. Of teenagers and adults who die, 30-40% have positive blood alcohol
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levels. Alcohol can impair judgment, leading to riskier behavior, decreased balance and coordination, and blunted ability to self-rescue. Furthermore, an intoxicated adult may provide less-effective supervision of children around water.

Sports and Recreation
Most drowning deaths in the United States occur during recreational activities. Drowning is the leading cause of noncardiac sports-related deaths. Surveys confirm that alcohol use is common during water recreation, as is not using a personal flotation device (PFD) during boating activities. In 2012, the United States Coast Guard reported that almost 90% of those who drowned in boating accidents in the United States were not wearing a PFD.

Global Impact of Drowning
Drowning injury is a significant problem for children worldwide, with the vast majority (96%) of fatalities occurring in low and middle income countries in Asia. Given the relative size of the pediatric population in many of these countries, drowning is one of the leading causes of death globally. A recent UNICEF study estimated that approximately 77,000 children in this region alone died from drowning between 2004 and 2008. This number vastly underestimates the global drowning rate, as many drowning deaths in this region go unreported, with 64–100% of those deaths being underreported in developing countries. Instead, significant locations for drowning in U.S. children, these are virtually unreported locations for drownings in developing countries. Instead, the predominant locations are near or around the home, involving bodies of water used for activities of daily living. These include water-collecting systems, ponds, ditches, creeks, and watering holes. In tropical areas, death rates increase during monsoon season, when ditches and holes rapidly fill with rain, and are highest during daylight hours, when caregivers are busy with daily chores.

Drowning during natural disasters such as storms and floods is important in all areas of the world. The largest numbers of reported flood-related deaths occur in developing nations; most are drownings that occur during the storm surge. In the United States and much of Europe, advances in weather monitoring and warning systems have reduced such deaths. U.S. flooding incidents, including hurricanes Katrina and Sandy, showed that drowning caused the most deaths, particularly when people became trapped in their vehicles, were unable or refused to evacuate homes, or attempted to rescue others.

PATHOPHYSIOLOGY
Drowning victims drown silently and do not signal distress or call for help. Vocalization is precluded by efforts to achieve maximal lung volume to keep the head above the water or by aspiration leading to laryngospasm. Young children can struggle for only 10–20 sec and adolescents for 30–60 sec before final submersion. A swimmer in distress is vertical in the water, pumping the arms up and down. This splashing or efforts to breathe are often misconstrued by nearby persons as merely “playing” in the water until the victim sinks.

Anoxic–Ischemic Injury
After experimental submersion, a conscious animal initially panics, trying to surface. During this stage, small amounts of water enter the hypopharynx, triggering laryngospasm. There is a progressive decrease in arterial blood oxygen saturation (SaO2), and the animal soon loses consciousness from hypoxia. Profound hypoxia and medullary depression lead to terminal apnea. At the same time, the cardiovascular response leads to progressively decreasing cardiac output and oxygen delivery to other organs. By 3–4 min, myocardial hypoxia leads to abrupt circulatory failure. Ineffective cardiac contractions with electrical activity may occur briefly, without effective perfusion (pulseless electrical activity). With early initiation of CPR, spontaneous circulation may initially be successfully restored. The extent of the global hypoxic–ischemic injury determines the final outcome and becomes more evident over subsequent hours.

With modern intensive care, the cardiorespiratory effects of resuscitated drowning victims are usually manageable and are less often the cause of death than irreversible hypoxic–ischemic central nervous system (CNS) injury (see Chapter 68). CNS injury is the most common cause of mortality and long-term morbidity. Although the duration of anoxia before irreversible CNS injury begins is uncertain, it is probably on the order of 3–5 min. Ninety percent of victims with reported submersions of less than 5 min survive and appear normal at hospital discharge.

Several hours after cardiopulmonary arrest, cerebral edema may occur, although the mechanism is not entirely clear. Severe cerebral edema can elevate intracranial pressure (ICP), contributing to further ischemia; intracranial hypertension is an ominous sign of profound CNS damage.

All other organs and tissues may exhibit signs of hypoxic–ischemic injury. In the lung, damage to the pulmonary vascular endothelium can lead to acute respiratory distress syndrome (see Chapter 71). Aspiration may also compound pulmonary injury. Myocardial dysfunction (so-called stunning), arterial hypotension, decreased cardiac output, arrhythmias, and cardiac infarction may also occur. Acute kidney injury, cortical necrosis, and renal failure are common complications of major hypoxic–ischemic events (see Chapter 535.1). Vascular endothelial injury may initiate disseminated intravascular coagulation, hemolysis, and thrombocytopenia. Many factors contribute to gastrointestinal damage; bloody diarrhea with mucosal sloughing may be seen and often portends a fatal injury. Serum levels of hepatic transaminases and pancreatic enzymes are often acutely increased. Violation of normal mucosal protective barriers predisposes the victim to bacteremia and sepsis.

Pulmonary Injury
Pulmonary aspiration (see Chapter 397) occurs in a majority of drowning victims, but the amount of aspirated fluid is usually small. Aspirated water does not obstruct airways and is readily moved into the


Anoxic–Ischemic Injury
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Pulmonary Injury
Pulmonary aspiration (see Chapter 397) occurs in a majority of drowning victims, but the amount of aspirated fluid is usually small. Aspirated water does not obstruct airways and is readily moved into the
pulmonary circulation with positive pressure ventilation. It can wash out surfactant and cause alveolar instability, ventilation-perfusion mismatch, and intrapulmonary shunting. In humans, aspiration of small amounts (1-3 mL/kg) can lead to marked hypoxemia and a 10-40% reduction in lung compliance. The composition of aspirated material can affect the patient’s clinical course: Gastric contents, pathogenic organisms, toxic chemicals, and other foreign matter can injure the lung or cause airway obstruction. Clinical management is not significantly different in saltwater and freshwater aspirations, because most victims do not aspirate enough fluid volume to make a clinical difference. A few children may have massive aspiration, increasing the likelihood of severe pulmonary dysfunction.

Cold Water Injury
Drowning should be differentiated from cold water immersion injuries, in which the victim remains afloat, keeping the head above water without respiratory impairment in cold waters. The definition of cold water varies from less than 15-20°C (59-68°F).

Heat loss through conduction and convection is more efficient in water than in air. Children are at increased risk for hypothermia because of their relatively high ratio of body surface area to mass, decreased subcutaneous fat, and limited thermogenic capacity. Hypothermia can develop as a result of prolonged surface contact with cold water during immersion, while the airway is above water, or with submersion. Body temperature may also continue to fall as a result of cold air, wet clothes, hypoxia, and hospital transport. Hypothermia in pediatric drowning victims may be observed even after drowning in relatively warm water and in warm climates.

Immersion in cold water has immediate respiratory and cardiovascular effects. Victims experience cold water shock, a dynamic series of cardiorespiratory physiologic responses that can cause drowning. In adults, immersion in icy water results in intense involuntary reflex hyperventilation and to a decrease in breath-holding ability to <10 sec, which leads to fluid aspiration. Severe bradycardia, the diving reflex, occurs in adults but is transient and rapidly followed by supraventricular and ectopic tachycardia and hypertension. There is no evidence that the diving reflex has any protective effect.

Even after surviving the chaotic minutes of cold water shock, after an additional 5-10 min of cold water immersion, the victim can become incapacitated. Cooling of large and small muscles disables the victim’s ability to grab hold, swim or perform other self-rescue maneuvers. Depending on water and air temperature, insulation, body surface area, thermogenic capacity, physical condition, swimming efforts, or high water flow rates, heat loss with continued immersion can significantly decrease core temperature to hypothermic levels within 30-60 min.

The symptoms and severity of hypothermia are categorized based on body temperature. The victim with mild hypothermia has a temperature of 34-36°C (93.2-96.8°F) with intact thermogenic mechanisms (shivering and nonshivering thermogenesis, vasoconstriction) and active movements. Compensatory mechanisms usually attempt to restore normothermia at body temperatures >32°C (89.6°F). Lower core temperatures lead to impaired cognition, coordination, and muscle strength and with it, less ability to self-rescue. Thermoregulation may fail and spontaneous rewarming will not occur. With moderate hypothermia (30 to <34°C [86 to <93.2°F]), loss of consciousness leads to water aspiration. Progressive bradycardia, impaired myocardial contractility, and loss of vasomotor tone contribute to inadequate perfusion, hypotension, and possible shock. At body temperatures <28°C (82.4°F), extreme bradycardia is usually present with decreases in cardiac output, and the propensity for spontaneous ventricular fibrillation or asystole is high. Central respiratory center depression with moderate to severe hypothermia results in hypoventilation and eventual apnea. A deep coma, with fixed and dilated pupils and absence of reflexes at very low body temperatures (<25-29°C [77-84.2°F]), may give the false appearance of death.

The brain can cool to a neuroprotective level if the cooling process is quick and cardiac output lasts long enough for sufficient heat loss to occur prior to the onset of severe hypoxia. However, if submersion leading to drowning occurs prior to development of a neuroprotective level of hypothermia, severe anoxia devastates tissue organs. The theoretical benefits, implications, and consequences of hypothermia in drowning victims are areas of controversy. Known adverse effects are associated with hypothermia, and these must be balanced against the potential benefits observed in experimental data. One should clearly differentiate among (a) controlled hypothermia, such as that used in the operating room before the onset of hypoxia or ischemia, (b) accidental hypothermia, such as occurs in drowning, which is uncontrolled and variable with onset during or shortly after hypoxia–ischemia, and (c) therapeutic hypothermia, involving the purposeful and controlled lowering and maintenance of body (or brain) temperature at some time after a hypoxic–ischemic event.

In drowning victims with uncontrolled accidental hypothermia associated with icy water submersion, there are a few case reports of good neurologic recovery after prolonged (10-150 min) cardiopulmonary arrest. Almost all of these rare survivors have been in freezing water (<5°C [41°F]) and had core body temperatures <30°C (86°F), often much lower. Presumably, very rapid and sufficiently deep hypothermia developed in these fortunate survivors before irreversible hypoxic–ischemic injury occurred.

Most often hypothermia is a poor prognostic sign, and a neuroprotective effect has not been demonstrated. In King County, Washington, where the water is cold but rarely icy, 92% of drowning survivors with good neurologic outcomes had initial body temperatures ≥34°C (93.2°F), whereas 61% of those who died or had severe neurologic injury had temperatures <34°C (93.2°F). In another study of comatose drowning patients admitted to pediatric intensive care units (PICUs), 65% of hypothermic patients (body temperature <35°C [95°F]) died, compared with a 27% observed mortality rate in nonhypothermic victims. Similarly, in Finland (where the median water temperature was 16°C [60.9°F]) and in the United States, a beneficial effect of drowning-associated hypothermia was not seen in pediatric submersion victims; submersion duration <10 min was most strongly related to good outcome, not water temperature.

MANAGEMENT
The clinical course and outcome for a submersion victim are primarily determined by the duration of submersion, the speed of the rescue, and the effectiveness of resuscitative efforts. Two groups may be identified on the basis of responsiveness at the scene. The first group consists of children who require minimal resuscitation at the scene and quickly regain spontaneous respiration and consciousness. They have good outcomes and minimal complications. These victims should be transported from the scene to the ED for further evaluation and observation.

The second group comprises children in cardiac arrest who require aggressive or prolonged resuscitation and have a high risk of multiorgan system complications, major neurologic morbidity, or death. Compared with cardiac arrest from other causes, cardiac arrest from drowning has a higher survival rate.

Initial management of drowning victims requires coordinated and experienced prehospital care following the ABCs (airway, breathing, circulation) of emergency resuscitation (see Chapter 67). Cardiopulmonary resuscitation of drowning victims must include providing ventilation. Children with severe hypoxic injury and symptoms often remain comatose and lack brainstem reflexes despite the restoration of oxygenation and circulation. Subsequent ED and PICU care often involve advanced life support strategies and management of multiorgan dysfunction.

Initial Evaluation and Resuscitation
See Chapter 67.

Once a submersion has occurred, immediate institution of CPR efforts at the scene is imperative. The goal is to reverse the anoxia from submersion and limit secondary hypoxic injury after submersion. Every minute that passes without the reestablishment of adequate
breathing and circulation dramatically decreases the possibility of a good outcome. When safe for the victim and the rescuer, institution of in-water resuscitation for nonbreathing victims by trained personnel may improve the likelihood of survival. Victims usually need to be extricated from the water as quickly as possible so that effective CPR can be provided. Common themes in children who have good recovery are a short duration of event and initiation of CPR as soon as possible, prior to arrival of emergency medical services.

**Initial resuscitation must focus on rapidly restoring oxygenation, ventilation, and adequate circulation.** The airway should be clear of vomitus and foreign material, which may cause obstruction or aspiration. Abdominal thrusts should not be used for fluid removal, because many victims have a distended abdomen from swallowed water; abdominal thrusts may increase the risk of regurgitation and aspiration. In cases of suspected airway foreign body, chest compressions or back blows are preferable maneuvers.

The cervical spine should be protected in anyone with potential traumatic neck injury (see Chapters 68 and 72). Cervical spine injury is a rare concomitant injury in drowning; only approximately 0.5% of submersion victims have cervical spine injuries. History of the event and victim age guide suspicion of cervical spine injury. Drowning victims with cervical spine injury are usually preteens or teenagers whose drowning event involved diving, a motorized vehicle crash, a fall from a height, a water sport accident, child abuse, or other clinical signs of serious traumatic injury. In such cases, the neck should be maintained in a neutral position and protected with a well-fitting cervical collar. Patients rescued from unknown circumstances may also warrant cervical spine precautions. In low-injury severity submersion, spinal injuries are exceedingly rare, and routine spinal immobilization is not warranted.

If the victim has ineffective respiration or apnea, ventilatory support must be initiated immediately (see Chapter 67). Mouth-to-mouth or mouth-to-nose breathing by trained bystanders often restores spontaneous ventilation. As soon as it is available, supplemental oxygen should be administered to all victims. Positive-pressure bag-mask ventilation with 100% inspired oxygen should be instituted in patients with respiratory insufficiency. If apnea, cyanosis, hypoventilation, or labored respiration persists, trained personnel should perform endotracheal tube intubation as soon as possible. Intubation is also indicated to protect the airway in patients with depressed mental status or hemodynamic instability. Hypoxia must be corrected rapidly to optimize the chance of recovery.

Concurrent with securing of airway control, oxygenation, and ventilation, the child's cardiovascular status must be evaluated and treated according to the usual resuscitation guidelines and protocols. Heart rate and rhythm, blood pressure, temperature, and end-organ perfusion require urgent assessment. CPR should be instituted immediately in pulseless, bradycardic, or severely hypotensive victims. Continuous monitoring of the electrocardiogram (ECG) allows appropriate diagnosis and treatment of arrhythmias. Slow capillary refill, cool extremities, and altered mental status are potential indicators of shock (see Chapter 70).

Recognition and treatment of hypothermia are the unique aspects of cardiac resuscitation in the drowning victim.** (Table 74-1). Core temperature must be evaluated, especially in children, because moderate to severe hypothermia can depress myocardial function and cause arrhythmias. Wet clothing should be removed to prevent ongoing heat losses, however, in the hemodynamically stable patient, rewarming should be initiated in the controlled environment of the receiving ED or PICU. Unstable patients (i.e. arrhythmias) should be warmed to 34°C (93.2°F), taking care not to overheat. Trials are investigating if therapeutic hypothermia might be helpful or if avoiding hyperthermia is actually the key element to long-term neurologic survival.

Often, IV fluids and cardiovascular medications are required to improve circulation and perfusion. Vascular access should be established as quickly as possible for the administration of fluids or pressors. Intravenous catheter placement is a potentially lifesaving vascular access technique that avoids the delay usually associated with multiple attempts to establish IV access in critically ill children. Epinephrine is usually the initial drug of choice in victims with bradycystolic cardiopulmonary arrest (the IV dose is 0.01 mg/kg of 1:10,000 solution given q3-5min as needed). Epinephrine can be given intratracheally (endotracheal tube dose is 0.1-0.2 mg/kg of 1:1,000 solution) if no IV access is available. An intravascular bolus of lactated Ringer solution or 0.9% normal saline (10-20 mL/kg) is often used to augment preload; repeated doses may be necessary. Hypotonic or glucose-containing solutions should not be used for intravascular volume administration of drowning victims.

**Hospital-Based Evaluation and Treatment**

Most pediatric drowning victims should be observed for at least 6-8 hr, even if they are asymptomatic on presentation to the ED. At a minimum, serial monitoring of vital signs (respiratory rate, heart rate, blood pressure, and temperature) and of oxygenation by pulse oximetry, and neurologic assessment should be performed in all drowning victims. Other studies may also be warranted, depending on the specific circumstances (possible abuse or neglect, traumatic injuries, or suspected intoxication). Almost half of asymptomatic or minimally symptomatic alert children (those who do not require advanced life support in the prehospital setting or who have an initial ED Glasgow Coma Scale [GCS] score of ≥13) experience some level of respiratory distress or hypoxemia progressing to pulmonary edema, usually during the 1st 4-8 hr after submersion. Most alert children with early respiratory symptoms respond to oxygen and, despite abnormal initial radiographs, become asymptomatic with a return of normal room air SaO₂ and pulmonary examination by 4-6 hr. Subsequent delayed respiratory deterioration is extremely unlikely in such children. Selected low-risk patients who are alert and asymptomatic with normal physical findings and oxygenation levels may be considered for discharge after 6-8 hr of observation, as long as appropriate follow-up can be ensured.

**Cardiorespiratory Management**

For children who are not in cardiac arrest, the level of respiratory support should be appropriate to the patient's condition and is a continuation of prehospital management. Frequent assessments are required to ensure that adequate oxygenation, ventilation, and airway control are maintained (see Chapter 71). Hypercapnia should generally be avoided in potentially brain-injured children. Patients with actual or potential hyperventilation or markedly elevated work of breathing should receive mechanical ventilation to avoid hypercapnia and decrease the energy expenditures of labored respiration.

Measures to stabilize cardiovascular status should also continue. Conditions contributing to myocardial insufficiency include hypoxic-ischemic injury, ongoing hypoxia, hypothermia, acidosis, high airway pressures during mechanical ventilation, alterations of intravascular volume, and electrolyte disorders. Heart failure, shock, arrhythmias, or cardiac arrest may occur. Continuous ECG monitoring is mandatory for recognition and treatment of arrhythmias (see Chapter 435).

The provision of adequate oxygenation and ventilation is a prerequisite to improving myocardial function. Fluid resuscitation and inotropic agents are often necessary to improve heart function and restore tissue perfusion (see Chapter 67). Increasing preload with IV fluids may be beneficial through improvements in stroke volume and cardiac output. Overzealous fluid administration, especially in the presence of poor myocardial function, can worsen pulmonary edema.

For patients with persistent cardiopulmonary arrest on arrival in the ED after non-icy water drowning, the decision to withhold or stop resuscitative efforts can be addressed by review of the history and the response to treatment. Because there are reports of good outcome following ongoing CPR in the ED, most drowning victims should be treated aggressively upon presentation. However, for children who do not show ready response to aggressive resuscitative efforts, the need for prolonged ongoing CPR after non-icy water submersion almost invariably predicts death or persistent vegetative state. Consequently, in most cases, discontinuation of CPR in the ED is probably warranted.
for victims of non–icy water submersion who do not respond to resuscitation within 25-30 min. Final decisions regarding whether and when to discontinue resuscitative efforts must be individualized, with the understanding that the possibility of good outcome is generally very low with protracted resuscitation efforts.

**Neurologic Management**

Drowning victims who present to the hospital awake and alert usually have normal neurologic outcomes. In comatose victims, irreversible CNS injury is highly likely. The most critical and effective neurologic intensive care measures after drowning are rapid restoration and maintenance of adequate oxygenation, ventilation, and perfusion. Core body temperature and glucose management may also be important modulators of neurologic injury after hypoxia–ischemia.

Comatose drowning patients are at risk for intracranial hypertension. There is little evidence that ICP monitoring and therapy to reduce intracranial hypertension improve outcomes for drowning victims. Patients with elevated ICP usually have poor outcomes—either death or persistent vegetative state. Children with normal ICP can also have poor outcomes, although less frequently. Conventional neurologic intensive care therapies, such as fluid restriction, hyperventilation, and administration of muscle relaxants, osmotic agents, diuretics, barbiturates, and steroids, have not been shown to benefit the drowning victim, either individually or in combination. There is some evidence that these therapies may reduce overall mortality but increase the number of survivors with severe neurologic morbidity.

Electroencephalographic monitoring has only limited value in the management of drowning victims and is generally not recommended, except to detect seizures or as an adjunct in the clinical evaluation of brain death (see Chapter 68.1). Seizures should be treated if possible, although they tend to be very refractory. There is no evidence that treatment of seizures after drowning improves outcome. Fosphenytoin or phenytoin (loading dose of 10-20 mg of phenytoin equivalents/kg, followed by maintenance dosing with 5-8 mg of phenytoin equivalents/kg/day in 2-3 divided doses; levels should be monitored) may be considered as an anticonvulsant; it may have some neuroprotective effects and may mitigate neurogenic pulmonary edema. Benzodiazepines, barbiturates, and other anticonvulsants may also have some role in seizure therapy.

With optimal management, many initially comatose children can have impressive neurologic improvement, but usually do so within the 1st 24-72 hr. Unfortunately, almost half of deeply comatose drowning victims admitted to the PICU die of their hypoxic brain injury or survive with severe neurologic damage. Many children become brain dead. Deeply comatose drowning victims who do not show substantial improvement on neurologic examination after 24-72 hr and whose coma cannot be otherwise explained should be seriously considered for limitation or withdrawal of support.

**Other Management Issues**

A few drowning victims may have traumatic injury (see Chapter 72), especially if their drowning event involved participation in high energy water sports such as personal watercraft, boating, diving, or surfing. A high index of suspicion for such injury is required. Spinal precautions should be maintained in victims with altered mental status and suspected traumatic injury. Significant anemia suggests trauma and internal hemorrhage.

Hyperoxic–ischemic injury can have multiple systemic effects, although protracted organ dysfunction is uncommon in the absence of severe CNS injury. Hyperglycemia is associated with a poor outcome in pediatric drowning victims. Its etiology is unclear but it is possibly a stress response.

Manifestations of acute kidney injury may be seen after hypoxic–ischemic injury (see Chapter 535). Diuretics, fluid restriction, and dialysis are occasionally needed to treat fluid overload or electrolyte disturbances; renal function usually normalizes in survivors. Rhabdomyolysis after drowning has been reported.

Profuse bloody diarrhea and mucosal sloughing usually portend a grim prognosis; conservative management includes bowel rest, nasogastric suction, and gastric pH neutralization. Nutritional support for most drowning victims is usually not difficult, because the majority of children either die or recover quickly and resume a normal diet within a few days; enteral tube feeding or parenteral nutrition is occasionally indicated in children who do not recover quickly.

Hyperthermia after drowning or other types of brain injury may increase the risk of mortality and exacerbate hypoxic–ischemic CNS damage. Almost half of drowning victims have a fever during the 1st 48 hr after submersion. Hyperthermia is usually not caused by

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**Table 74-1** Approach to Drowning-Prevention Strategies

<table>
<thead>
<tr>
<th>HOME</th>
<th>RECREATION</th>
<th>NEIGHBORHOOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water hazards</td>
<td>Swimming pools</td>
<td>Playing in water—swimming, wading</td>
</tr>
<tr>
<td></td>
<td>Ponds</td>
<td>Playing near water—boating</td>
</tr>
<tr>
<td></td>
<td>Bathtubs</td>
<td>Being on water—boating</td>
</tr>
<tr>
<td></td>
<td>Large buckets</td>
<td></td>
</tr>
<tr>
<td>Common risks</td>
<td>Lapse in supervision</td>
<td>Lapse in supervision</td>
</tr>
<tr>
<td></td>
<td>Unexpected toddler exposure</td>
<td>Change in weather</td>
</tr>
<tr>
<td></td>
<td>Delayed discovery of child</td>
<td>Unfamiliarity with or change(s) in water</td>
</tr>
<tr>
<td></td>
<td>Reliance on water wings or pool toys</td>
<td>conditions:</td>
</tr>
<tr>
<td></td>
<td>Reliance on sibling or bath seat for</td>
<td>• Steep drop-off</td>
</tr>
<tr>
<td></td>
<td>bathing supervision</td>
<td>• Current/tide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Low temperature</td>
</tr>
<tr>
<td>Prevention</td>
<td></td>
<td>Alcohol use</td>
</tr>
<tr>
<td>strategies</td>
<td></td>
<td>Peer pressure</td>
</tr>
<tr>
<td></td>
<td>Recognize hazards and risks</td>
<td>Provide constant adult supervision</td>
</tr>
<tr>
<td></td>
<td>Provide constant adult supervision</td>
<td>around water</td>
</tr>
<tr>
<td></td>
<td>Install 4-sided, isolation fencing of</td>
<td>Know when and how to wear U.S. Coast</td>
</tr>
<tr>
<td></td>
<td>pools</td>
<td>Guard–approved PFDs</td>
</tr>
<tr>
<td></td>
<td>Install rescue equipment and phone at</td>
<td>Avoid alcohol and other drugs</td>
</tr>
<tr>
<td></td>
<td>poolside</td>
<td>Learn swimming and water survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td>skills</td>
</tr>
<tr>
<td></td>
<td>Learn swimming and water survival</td>
<td>Teach children about water safety</td>
</tr>
<tr>
<td></td>
<td>skills</td>
<td>Be aware of current weather and water</td>
</tr>
<tr>
<td></td>
<td>Avoid bath, instead shower, if a child/</td>
<td>conditions</td>
</tr>
<tr>
<td></td>
<td>teen with seizure disorder</td>
<td>Learn first aid and CPR</td>
</tr>
<tr>
<td></td>
<td>Learn first aid and CPR</td>
<td></td>
</tr>
</tbody>
</table>

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**Chapter 74 – Drowning and Submersion Injury**

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infection and resolves without antibiotics in approximately 80% of patients. Generally, prophylactic antibiotics are not recommended. However, there is general consensus that fever or hyperthermia (core body temperature >37.5°C [99.5°F]) in comatose drowning victims resuscitated from cardiac arrest should be prevented at all times in the acute recovery period (at least the 1st 24-48 hr).

Psychiatric and psychosocial sequelae in the family of a pediatric drowning victim are common. Grief, guilt, and anger are common among family members, including siblings. Divorce rates of up to 80% within a few years of the injury have been reported, and parents often report difficulties with employment or substance abuse. Friends and family may blame the parents for the event. Professional counseling, pastoral care, or social work referral should be initiated for drowning victims and their families.

Hypothermia Management

Attention to core body temperature starts in the field and continues during transport and in the hospital. The goal is to prevent or treat moderate or severe hypothermia. Damp clothing should be removed from all drowning victims. Rewarming measures are generally categorized as passive, active external, or active internal (see Chapter 76). Passive rewarming measures can be applied in the prehospital or hospital setting; they include the provision of dry blankets, a warm environment, and protection from further heat loss. They should be instituted as soon as possible for hypothermic drowning victims who have not had a cardiac arrest.

Full CPR with chest compressions is indicated for hypothermic victims if no pulse can be found or if narrow complex QRS activity is absent on ECG (see Chapters 67 and 76). When core body temperature is <30°C (86°F), resuscitative efforts should proceed according to the current American Heart Association guidelines for CPR, but IV medications may be given at a lower frequency in moderate hypothermia because of decreased drug clearance. When ventricular fibrillation is present in severely hypothermic victims (core temperature <30°C [86°F]), defibrillation should be initiated but may not be effective until the core temperature is ≥30°C (86°F), at which time successful defibrillation may be more likely.

Significant controversy surrounds the discontinuation of prolonged resuscitative efforts in hypothermic drowning victims. Body temperature should be taken into account before resuscitative efforts are terminated. Other considerations include whether the victim may have been immersed prior to submersion, whether water was icy or the cooling was very rapid with fast-flowing cold water. Victims with profound hypothermia may appear clinically dead, but full neurologic recovery is possible, although rare. Attempts at lifesaving resuscitation should not be withheld on the basis of initial clinical presentation unless the victim is obviously dead (dependent lividity or rigor mortis). Rewarming efforts should usually be continued until the temperature is 32-34°C (89.6-93.2°F); if the victim continues to have no effective cardiac rhythm and remains unresponsive to aggressive CPR, then resuscitative efforts may be discontinued.

Complete rewarming is not indicated for all arrest victims before resuscitative efforts are abandoned. Discontinuing resuscitation in victims of non-icy water submersion who remain asyptic despite 30 min of CPR is probably warranted. Physicians must use their individual clinical judgment about deciding to stop resuscitative efforts, taking into account the unique circumstances of each incident.

Once a drowning victim has undergone successful CPR after a cardiac arrest, temperature management should be carefully considered, and body temperature should be continuously monitored. In victims in whom resuscitation duration was brief and who are awake soon after resuscitation, attempts to restore and maintain normothermia are warranted. Careful monitoring is necessary to prevent unrecognized worsening hypothermia, which can have untoward consequences.

For drowning victims who remain comatose after successful CPR, more contentious issues include rewarming of hypothermic victims and controlled application of therapeutic hypothermia. Although there is no evidence basis or consensus of opinion, many investigators cautiously recommend that hypothermic drowning victims who remain unresponsive because of hypoxic-ischemic encephalopathy after restoration of adequate spontaneous circulation should not be actively rewarmed to normal body temperatures. Active rewarming should be limited to victims with core body temperatures <32°C (89.6°F), but temperatures 32-37.5°C (89.6-99.5°F) should be allowed without further rewarming efforts.

More controversial is the induction of therapeutic hypothermia in drowning victims who remain comatose because of hypoxic-ischemic encephalopathy after CPR for cardiac arrest. The 2002 World Congress on Drowning recommended that hypothermia (32-34°C [89.6-93.2°F]) be instituted as soon as possible after resuscitation and sustained for 12-24 hr. They recommended that patients be intubated, mechanically ventilated, and treated with sedatives and/or analgesics (with or without neuromuscular blocking agents) as necessary to prevent shivering and maintain hypothermia then gradually rewarmed.

However, a specific recommendation for therapeutic hypothermia, especially in children, is not yet generally accepted. The Advanced Life Support Task Force of the International Liaison Committee on Resuscitation (2002) did not recommend therapeutic hypothermia in drowned children resuscitated after cardiopulmonary arrest, citing insufficient evidence and older studies demonstrating a potential deleterious effect in pediatric drowning victims. Several subsequent studies evaluating extracorporeal membrane circulation, rewarming, and therapeutic hypothermia in pediatric and adult drowned patients have shown no significant improvement in neurologic outcome or mortality rates.

PROGNOSIS

The outcomes for drowning victims are remarkably bimodal: The great majority of victims either have a good outcome (intact or mild neurologic sequelae) or a bad outcome (severe neurologic sequelae, persistent vegetative state or death), with very few exhibiting intermediate neurologic injury at hospital discharge. Subsequent evaluation of good outcome survivors may identify significant persistent cognitive deficits. Of hospitalized pediatric drowning victims, 15% die and as many as 20% survive with severe permanent neurologic damage.

Strong predictors of outcome are based on the incident and response to treatment at the scene. Intact survival or mild neurologic impairment has been seen in 91% of children with submersion duration ≤5 min and in 87% with resuscitation duration ≤10 min. Children with normal sinus rhythm, reactive pupils, or neurologic responsiveness at the scene virtually always had good outcomes (99%). Poor outcome is highly likely in patients with deep coma, apnea, absence of papillary responses, and hyperglycemia in the ED, with submersion durations ≥10 min, and with failure of response to CPR given for ≥25 min. In one comprehensive case series, all children with resuscitation durations ≥25 min either died or had severe neurologic morbidity, and all victims with submersion durations ≥25 min died.

Long-term health-related quality of life and school performance in subjects who had received either bystander or emergency medical service personnel initiated CPR was high if their submersion duration was <10 mins. Higher morbidity, mortality, and lower quality of life was reported in those patients with >10 mins submersion durations. In several studies of pediatric drowning, submersion duration was the best predictor of outcome and water temperature was not. However, there are rare case reports of intact recovery following non-icy water drowning with longer submersion or resuscitation duration.

The GCS score has some limited utility in predicting recovery. Children with a score ≥6 on hospital admission generally have a good outcome, whereas those with a score ≤5 have a much higher probability of poor neurologic outcome. Occasionally, children with a GCS score of 3 or 4 in the ED have complete recovery. Improvement in the GCS score during the first several hours of hospitalization may indicate a better prognosis. Overall, early GCS assessments fail to adequately
distinguish children who will survive intact from those with major neurologic injury.

Neurologic examination and progression during the 1st 24-72 hr are the best prognosticators of long-term CNS outcome. Children who regain consciousness within 48-72 hr, even after prolonged resuscitation, are unlikely to have serious neurologic sequelae. In a small series of comatose victims of non–icy water submersion, all survivors with a good outcome had spontaneous purposeful movements and normal brainstem function within 24 hr; good recovery did not occur in any child with abnormal brainstem function or absence of purposeful movements at 24 hr. In another small series of drowning victims who remained unconscious >24 hr and survived for at least 1 yr, 73% remained in a persistent vegetative state and the rest had severe neurologic impairment, had many complications and a high mortality rate: 45% died during the study’s 1-yr follow-up period.

In a large retrospective series of 274 pediatric drowning victims, of those with an initial GCS score of 3 in the ED, only 14% survived intact. Almost all, 95%, of victims who demonstrated purposeful neurologic function within 48 hr survived intact and 100% of those whose first purposeful neurologic response occurred within 6 hr survived intact. Laboratory and technologic methods to improve prognostication have not yet proved superior to neurologic examination. Serial neurologic evaluations after CPR should be performed over the ensuing 48-72 hr, with consideration given to limitation or withdrawal of support in patients who do not have significant neurologic recovery, even though this may occur before absolute prognostic certainty is achieved.

**PREVENTION**

The most effective way to decrease the injury burden of drowning is prevention. Drowning is a multifaceted problem, but several evidence-based preventive strategies are effective. The pediatrician has a prime opportunity to identify and inform families at risk of these strategies through anticipatory guidance. In 2010, the American Academy of Pediatrics Committee on Injury, Violence, and Poison Prevention revised its policy statement on the prevention of drowning to advocate for more anticipatory guidance regarding the appropriate supervision of children, access to swim lessons, the presence of lifeguards, barriers to swimming pools, and use of PFDs. A family-centered approach to anticipatory guidance for water safety helps explore and identify the water hazards that each family is exposed to in their environment. The practitioner can then discuss the best tools and strategies for prevention that are relevant for the particular family. It is important to identify the risks both in and around the home and in other locations they may frequent, often when vacationing, such as vacation or relatives’ homes. For some families the focus may be on bathtubs and bucket safety; for others, home pools or hot tubs may be the major hazards. If the family recreates near or on open water, they also need to learn about safety around boats and open water. In a rural environment, water collection systems and natural bodies of water may pose great risk.

Parents must build layers of water protection around their children. **Table 74-1** provides an approach to the hazards and preventive strategies relevant to the most common sources of water involved in childhood drowning. A common preventive strategy for exposure to all water types and all ages is ensuring appropriate supervision. Pediatricians should define for parents what constitutes appropriate supervision at the various developmental levels of childhood. Many parents either underestimate the importance of adequate supervision or are simply unaware of the risks associated with water. Even parents who say that constant supervision is necessary will often admit to brief lapses while their child is alone near water. Parents also overestimate the abilities of older siblings; many bathtub drownings occur when an infant or toddler is left with a child younger than 5 yr.

Supervision of infants and young children means that a responsible adult should be with the child every moment. The caregiver must be alert, must not be consuming alcohol or other drugs or socializing, and must be attentive and focused entirely on watching the child. Even a brief moment of inattention, such as to answer a phone, get a drink, or hold a conversation, can have tragic consequences. If the child does not swim, “touch supervision” is required, meaning that the caregiver should be within arm’s reach at all times. Adolescents require active adult supervision and avoidance of alcohol or drug use during water activities. Learning to swim offers another layer of protection. Children may start swim lessons at an early age that are developmentally appropriate and aimed at the individual child’s readiness and skill level. Swim lessons are beneficial and to provide some level of protection to young children. A study from Bangladesh, where drowning accounts for 20% of all deaths in children ages 1-4 yr, showed that swim lessons and water safety curricula are cost-effective and led to a decrease in mortality from drowning. As with any other water safety intervention, parents need to know that swimming lessons and acquisition of swim skills cannot be solely relied on to prevent drowning. No child can be “drown-proof.” A supervising caretaker should be aware of where and how to get help and know how to safely rescue a child in trouble. Because only those trained in water rescue can safely attempt it, families should be encouraged to swim in designated areas only when and where a lifeguard is on duty.

Children and adolescents should never swim alone regardless of their swimming abilities. Even as they become more independent and participate in recreational activities without their parents, they should be encouraged to seek areas that are watched by lifeguards. Lifeguards rescue more than 100,000 Americans each year from drowning, and probably prevent millions more drownings through verbal warnings and prompt interventions when needed. It is important to emphasize that even if the child is considered a strong swimmer, the ability to swim in a pool does not translate to being safe in open water, where water temperature, currents, and underwater obstacles can present additional and unfamiliar challenges. For swimmers, supervision by lifeguards reduces drowning risk, because lifeguards monitor risk behaviors and are trained in the difficult and potentially dangerous task of rescuing drowning victims.

Two of the preventive strategies listed in **Table 74-1** deserve special mention. The most vigorously evaluated and effective drowning intervention applies to swimming pools. Isolation fencing that completely surrounds a pool, with a secure, self-locking gate, reduces the risk of drowning. Guidelines for appropriate fencing, provided by the U.S. Consumer Product Safety Commission, are very specific; they were developed through testing of active toddlers in a gymnastics program on their ability to climb barriers of different materials and heights and recent studies show them to be effective in preventing drowning in young children. In families who have a pool on their property, caregivers often erroneously believe that if a child falls into the water there will be a loud noise or splash to alert them. Sadly, these events are usually silent, delaying timely rescue. This finding highlights the need for a fence that actually separates the pool from the house, not just surrounds the entire property. The use of U.S. Coast Guard–approved lifejackets or PFDs should be advised with all families spending time around open water, not just those who consider themselves boaters. This issue is also particularly important for families who will participate in aquatic activities on a vacation. A PFD should be chosen with respect to the weight of the child and the proposed activity. Young children should wear PFDs that will float their head up. Parents should be urged to wear PFDs, too, as their use is associated with greater use by their children. Toys such as water wings and “floaties” should not be relied upon as drowning prevention measures.

Effective preventive efforts must also consider cultural practices. Different ethnic groups may have certain attitudes, beliefs, dress, or other customs that may affect their water safety. The higher drowning risk of minority children needs to be addressed by community-based prevention programs. In addition to anticipatory guidance, pediatricians can play an active role in drowning prevention by participating in advocacy efforts to
improve legislation for pool fencing, PFD use, and alcohol consumption in various water activities. Several counties in the United States, Australia, and New Zealand have laws requiring isolation fencing for pools. Their effectiveness has been limited by a lack of enforcement. Similarly, all states have boating-under-the-influence laws but, similarly, rarely enforce them. Furthermore, efforts at the community level may be needed to ensure the availability of swimming lessons for underserved populations and lifeguarded swim areas.

_Bibliography is available at Expert Consult._
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Bibliography


Burns are a leading cause of unintentional injury in children, second only to motor vehicle crashes. There has been a decline in the incidence of burn injury requiring medical care that has coincided with a stronger focus on burn treatment and prevention, increased fire and burn prevention education, greater availability of regional treatment centers, widespread use of smoke detectors, greater regulation of consumer products and occupational safety, and societal changes such as reductions in smoking and alcohol abuse.

EPIDEMIOLOGY

Approximately 2 million people in the United States require medical care for burn injuries each year. Approximately 50% of these patients are younger than age 5 yr, with an average age of 32 mo. The principal cause of the burn is scald; one of the causes of scald burn is heating liquids in the microwave. The leading cause of burn in children 5-14 yr of age is flame injury. In children ages 5-10 yr, this is usually a result of match play, whereas, for older children, it is usually a result of gasoline ignition. Fires are a major cause of mortality in children, accounting for up to 34% of fatal injuries in those younger than age 16 yr. Scald burns account for 85% of total injuries and are most prevalent in children younger than 4 yr. Although the incidence of hot water scalding has been reduced by legislation requiring new water heaters to be preset at 48.9°C (120°F), scald injury remains the leading cause of hospitalization for burns. Steam inhalation used as a home remedy to treat respiratory infections is another potential cause of burns. Flame burns account for 13%; the remaining are electrical and chemical burns. Clothing ignition events have declined since passage of the Federal Flammable Fabric Act requiring sleepwear to be flame-retardant; however, the U.S. Consumer Product Safety Commission has voted to relax the existing children’s sleepwear flammability standard. Polyester is the fabric most resistant to ignition by small flame source. Polyester does burn deeply as it melts, but it self-extinguishes when the flame source is removed. Cotton, on the other hand, continues to burn after the flame source has been removed resulting in large deep burns. Polyester melts downward, sparing the face and respiratory tract; cotton burns upward toward the face. Pellet stove, glass front stoves, and flat top stoves are becoming frequent sources of hand burns in children. Approximately 18% of burns are the result of child abuse (usually scalds), making it important to assess the pattern and site of injury and their consistency with the patient history (see Chapter 40). Friction burns from treadmills are also a problem. Hands are the most commonly injured sites, with deep 2nd-degree friction injury sometimes associated with fractures of the fingers. Anoxia, not the actual burn, is a major cause of morbidity and mortality in house fires.

Review of the history usually shows a common pattern: scal burns to the side of the face, neck, and arm if liquid is pulled from a table or stove; burns in the pant leg area if clothing ignites; burns in a splash pattern from cooking; and burns on the palm of the hand from contact with a hot stove. However, “glove or stocking” burns of the hands and feet, single-area deep burns on the trunk, buttocks, or back, and small, full-thickness burns (cigarette burns) in young children should raise the suspicion of child abuse (see Chapter 40).

Burn care involves a range of activities: prevention, acute care and resuscitation, wound management, pain relief, reconstruction, rehabilitation, and psychosocial adjustment. Children with massive burns require early and appropriate psychological and social support as well as resuscitation. Surgical debridement, wound closure, and rehabilitative efforts should be instituted concurrently to promote optimal rehabilitation. Aggressive surgical removal of devitalized tissue, infection control, and judicious use of antibiotics, as well as early nutrition and cautious use of intubation and mechanical ventilation, are necessary to maximize survival. Children who have sustained burn injuries differ in appearance from their peers, necessitating supportive efforts for reentry to school and social and sporting activities.

PREVENTION

The aim of burn prevention is a continuing reduction in the number of serious burn injuries (Table 75-1). Effective first aid and triage can decrease both the extent (area) and the severity (depth) of injuries. The use of flame-retardant clothing and smoke detectors, control of hot water temperature (thermostat settings) to 48.9°C (120°F) within buildings, and prohibition of cigarette smoking have been partially successful in reducing the incidence of burn injuries. Treatment of children with significant burn injuries in dedicated burn centers facilitates medically effective care, improves survival, and leads to greater cost efficiency. Survival of at least 80% of patients with burns of 90% of the body surface area (BSA) is possible; the overall survival rate of children with burns of all sizes is 99%. Death is more likely in children with irreversible anoxic brain injury sustained at the time of the burn. It is well-known that burns occur in predictable patterns. Seasonal pattern sources include:

Winter
- Glass front fireplaces/pellet stoves and radiators increase hand burns
- Treadmill injuries as more people exercise inside—child imitates adults or young child touches belt

Summer
- Fireworks, sparkler—temperatures reach 537.8°C (1000°F)
- Burn contact with hot grill; hand/feet burn from hot embers
- Lawnmowers

Spring/Fall
- Burning leaves
- Gasoline burns
- Tap water scalds are essentially preventable through a combination of behavioral and environmental changes

Pediatricians can play a major role in preventing the most common burns by educating parents and healthcare providers. Simple, effective, efficient, and cost-effective preventive measures include the use of appropriate clothing and smoke detectors, and the planning of routes for emergency exit from the home. The National Fire Protection Association (NFPA) recommends replacing smoke detector batteries annually and the smoke detector alarm every 10 yr (or earlier, if indicated on the device). Child neglect and abuse must be seriously considered when the history of the injury and the distribution of the burn do not match.

ACUTE CARE, RESUSCITATION, AND ASSESSMENT

Indications for Admission

Burns covering >10% of total BSA, burns associated with smoke inhalation, burns resulting from high-tension (voltage) electrical injuries,
Burn Prophylaxis

**PREVENT FIRES**
Install and use smoke detectors
Control the hot water thermostat—in public buildings, the maximum water temperature should be 48.9°C (120°F)
Keep fire, matches, and lighters out of the reach of children
Avoid cigarette smoking, especially in bed
Do not leave lit candles unattended
Use flame retardant–treated clothing
Use caution when cooking, especially with oil
Keep cloth items off heaters

**PREVENT INJURY**
Roll, but do not run, if clothing catches fire; wrap in a blanket
Practice escape procedures
Crawl beneath smoke if a fire occurs indoors
Use educational materials*

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**Table 75-1** Burn Prophylaxis

<table>
<thead>
<tr>
<th>Prevent Fires</th>
<th>Prevent Injuries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Install and use smoke detectors.</td>
<td>Roll, but do not run, if clothing catches fire; wrap in a blanket.</td>
</tr>
<tr>
<td>Control the hot water thermostat—in public buildings, the maximum water temperature should be 48.9°C (120°F).</td>
<td>Practice escape procedures.</td>
</tr>
<tr>
<td>Keep fire, matches, and lighters out of the reach of children.</td>
<td>Crawl beneath smoke if a fire occurs indoors.</td>
</tr>
<tr>
<td>Avoid cigarette smoking, especially in bed.</td>
<td>Use educational materials*.</td>
</tr>
<tr>
<td>Use flame retardant–treated clothing.</td>
<td>Prevent burns to the face, hands, feet, perineum, genitals, or major joints.</td>
</tr>
<tr>
<td>Use caution when cooking, especially with oil.</td>
<td>Burns affecting &gt;10% of BSA.</td>
</tr>
<tr>
<td>Keep cloth items off heaters.</td>
<td>Burns &gt;10-20% of BSA in adolescent/adult.</td>
</tr>
</tbody>
</table>

**Table 75-2** Indications for Hospitalization for Burns

<table>
<thead>
<tr>
<th>Burns affecting &gt;10% of BSA</th>
<th>Burns &gt;10-20% of BSA in adolescent/adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burns &gt;15% of BSA in children</td>
<td>Burns &gt;5% of BSA in children</td>
</tr>
<tr>
<td>3rd-Degree burns</td>
<td>Electrical burns caused by high-tension wires or lightning</td>
</tr>
<tr>
<td>Chemical burns</td>
<td>Inhalation injury, regardless of the amount of BSA burned</td>
</tr>
<tr>
<td>Inadequate home or social environment</td>
<td>Suspected child abuse or neglect</td>
</tr>
<tr>
<td>Associated injuries (fractures)</td>
<td>Burns to the face, hands, feet, perineum, genitals, or major joints</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Burns in patients with preexisting medical conditions that may complicate the acute recovery phase</td>
</tr>
</tbody>
</table>

**First Aid Measures**

Acute care should include the following measures:

1. Extinguish flames by rolling the child on the ground; cover the child with a blanket, coat, or carpet.
2. After determining that the airway is patent, remove smoldering clothing or clothing saturated with hot liquid. Jewelry, particularly rings and bracelets, should be removed or cut away to prevent constriction and vascular compromise during the edema phase in the 1st 24-72 hr after burn injury.
3. In cases of chemical injury, brush off any remaining chemical, if powdered or solid; then use copious irrigation or wash the affected area with water. Call the local poison control center for the neutralizing agent to treat a chemical ingestion.
4. Cover the burned area with clean, dry sheeting and apply cold (not iced) wet compresses to small injuries. Significant large-burn injury (>15% of BSA) decreases body temperature control and contraindicates the use of cold compresses.
5. If the burn is caused by hot tar, use mineral oil to remove the tar.
6. Administer analgesic medications.

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**Table 75-3** Acute Treatment of Burns

| First aid, including washing of wounds and removal of devitalized tissue |
|--------------------------|----------------------|
| Fluid resuscitation | Provision of energy requirements |
| Life-support measures | Control of pain |
| Prevention of infection—early excision and grafting | Prevention of excessive metabolic expenditures |
| Control of bacterial wound flora | Use of biologic and synthetic dressings to close the wound |

**Emergency Care**

Life-support measures are as follows (Table 75-3):

1. Rapidly review the cardiovascular and pulmonary status and document pre-existing or physiologic lesions (asthma, congenital heart disease, renal or hepatic disease).
2. Ensure and maintain an adequate airway and provide humidified oxygen by mask or endotracheal intubation (Fig. 75-1). The latter may be needed in children who have facial burns or a burn sustained in an enclosed space, before facial or laryngeal edema becomes evident. If hypoxia or carbon monoxide poisoning is suspected, 100% oxygen should be used (see Chapters 67 and 71).
3. Children with burns >15% of BSA require intravenous (IV) fluid resuscitation to maintain adequate perfusion. In an emergency situation if IV access is unattainable, an intraosseous line should be placed. When inserting central lines to provide high-volume fluid, special attention should be paid to use a very-small-caliber catheter in small children to avoid injury to the vascular lining, which may predispose to formation of clots. All inhalation injuries, regardless of the extent of BSA burn, require venous access to control fluid intake. All high-tension and electrical injuries require venous access to ensure forced alkaline diuresis in case of muscle injury to avoid myoglobinuric renal damage. Lactated Ringer solution, 10-20 mL/kg/hr (normal saline may be used if lactated Ringer solution is not available), is initially infused until proper fluid replacement can be calculated. Consultation with a specialized burn unit should be made to coordinate fluid therapy, the type of fluid, the preferred formula for calculation, and preferences for the use of colloid agents, particularly if transfer to a burn center is anticipated.
4. Evaluate the child for associated injuries, which are common in patients with a history of high-tension electrical burn, especially if there has also been a fall from a height. Injuries to the spine, bones, and thoracic or intraabdominal organs may occur (see Chapter 72). Cervical spine precautions should be observed until this injury is ruled out. There is a very high risk of cardiac abnormalities, including ventricular tachycardia and ventricular fibrillation, resulting from conductivity of the high electric voltage. Cardiopulmonary resuscitation should be instituted promptly at the scene, and cardiac monitoring should be started upon the patient’s arrival at the emergency department (see Chapter 67).
5. Children with burns of >15% of BSA should not receive oral fluids (initially), because gastric distention may develop. These children require insertion of a nasogastric tube in the emergency department to prevent aspiration. A Foley catheter should be inserted to monitor urine output in all children who require IV fluid resuscitation.
6. All wounds should be wrapped with sterile dressings until a decision is made about whether to treat the patient on an outpatient basis or refer the patient to an appropriate facility for treatment.
7. A carbon monoxide measurement (carboxyhemoglobin [HbCO]) should be obtained for fire victims, and 100% oxygen administered until the result is known.

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*National Fire Protection Association pamphlets and videos.
Classification of Burns

Proper triage and treatment of burn injury require assessment of the extent and depth of the injury (Table 75-4 and Fig. 75-2). First-degree burns involve only the epidermis and are characterized by swelling, erythema, and pain (similar to mild sunburn). Tissue damage is usually minimal, and there is no blistering. Pain resolves in 48-72 hr; in a small percentage of patients, the damaged epithelium peels off, leaving no residual scars.

A 2nd-degree burn involves injury to the entire epidermis and a variable portion of the dermal layer (vesicle and blister formation are characteristic). A superficial 2nd-degree burn is extremely painful because a large number of remaining viable nerve endings are exposed. Superficial 2nd-degree burns heal in 7-14 days as the epithelium regenerates in the absence of infection. Midlevel to deep 2nd-degree burns also heal spontaneously if wounds are kept clean and infection-free. Pain is less than in more superficial burns because fewer nerve endings remain viable. Fluid losses and metabolic effects of deep dermal (2nd-degree) burns are essentially the same as those of 3rd-degree burns.

Full-thickness, or 3rd-degree, burns involve destruction of the entire epidermis and dermis, leaving no residual epidermal cells to repopulate the damaged area. The wound cannot epithelialize and can heal only by wound contraction or skin grafting. The absence of painful sensation and capillary filling demonstrates the loss of nerve

Figure 75-1 Algorithm for the primary survey of a major burn injury. O₂, oxygen. (From Hettiaratchy S, Papini R: Initial management of a major burn I: overview. BMJ 328:1555-1557, 2004.)
and capillary elements. The use of Doppler scanner has become a valuable adjunct tool in burn depth assessment and burn healing potential.

**Estimation of Body Surface Area for a Burn**

Appropriate burn charts for different childhood age groups should be used to accurately estimate the extent of BSA burned. The volume of fluid needed in resuscitation is calculated from the estimation of the extent and depth of burn surface. Mortality and morbidity also depend on the extent and depth of the burn. The variable growth rate of the head and extremities throughout childhood makes it necessary to use BSA charts, such as that modified by Lund and Brower or the chart used at the Shriners Hospital for Children in Boston (Fig. 75-3). The rule of nines used in adults may be used only in children older than 14 yr or as a very rough estimate to institute therapy before transfer to a burn center. In small burns, <10% of BSA, the rule of palm may be used, especially in outpatient settings: The area from the wrist crease to the finger crease (the palm) in the child equals 1% of the child's BSA.

**TREATMENT**

**Outpatient Management of Minor Burns**

A patient with 1st- and 2nd-degree burns of <10% of BSA may be treated on an outpatient basis unless family support is judged inadequate or there are issues of child neglect or abuse. These outpatients do not require a tetanus booster (unless not fully immunized) or prophylactic penicillin therapy. Blisters should be left intact and dressed with bacitracin ointment and left open. Debridement of the devitalized skin is indicated when the blisters rupture. A variety of wound dressings/wound membranes are available (e.g., AQUACEL Ag dressing [Convatec USA, Skillman, NJ] in a soft felt-like material impregnated with silver ion) may be applied to 2nd-degree burns and wrapped with a dry sterile dressing; similar wound membranes provide pain control, prevention of wound desiccation, and reduction in wound colonization (Table 75-5). These dressings are usually kept on for 7-10 days but are checked twice a week.

Burns to the palm with large blisters usually heal beneath the blisters; they should receive close follow-up on an outpatient basis. The great majority of superficial burns heal in 10-20 days. Deep 2nd-degree burns take longer to heal and may benefit from enzymatic debridement ointment application (collagenase ointment) applied daily on the wound, which aids in the removal of the dead tissue. These ointments should not be applied to the face to avoid the risk of getting them into the eyes.

The depth of scald injuries is difficult to assess early; conservative treatment is appropriate initially, with the depth of the area involved

### Table 75-4 Categories of Burn Depth

<table>
<thead>
<tr>
<th>1ST-DEGREE BURN</th>
<th>2ND-DEGREE, OR PARTIAL-THICKNESS, BURN</th>
<th>3RD-DEGREE, OR FULL-THICKNESS, BURN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface appearance</td>
<td>Moist blebs, blisters</td>
<td>Dry, leathery eschar</td>
</tr>
<tr>
<td></td>
<td>Underlying tissue is mottled pink and white, with fair capillary refill</td>
<td>Mixed white, waxy, khaki, mahogany, soot-stained</td>
</tr>
<tr>
<td></td>
<td>Bleeds</td>
<td>No blanching or bleeding</td>
</tr>
<tr>
<td>Pain</td>
<td>Very painful</td>
<td>Very painful</td>
</tr>
<tr>
<td>Histologic depth</td>
<td>Epidermal layers only</td>
<td>Epidermis, papillary, and reticular layers of dermis</td>
</tr>
<tr>
<td></td>
<td>May include domes of subcutaneous layers</td>
<td>Down to and may include fat, subcutaneous tissue, fascia, muscle, and bone</td>
</tr>
<tr>
<td>Healing time</td>
<td>2-5 days with no scarring</td>
<td>Superficial: 5-21 days with no grafting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deep partial: 21-35 days with no infection; if infected, converts to full-thickness burn</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Large areas require grafting, but small areas may heal from the edges after wks</td>
</tr>
</tbody>
</table>

### Table 75-5 Partial Listing of Some Commonly Used Wound Membranes—Selected Characteristics

<table>
<thead>
<tr>
<th>MEMBRANE</th>
<th>CHARACTERISTIC(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porcine xenograft</td>
<td>Adheres to coagulum; Excellent pain control</td>
</tr>
<tr>
<td>Biobrane</td>
<td>Bilaminate; Fibrovascular in growth into inner layer</td>
</tr>
<tr>
<td>Acticoat</td>
<td>Nonadherent dressing that delivers silver</td>
</tr>
<tr>
<td>AQUACEL-Ag</td>
<td>Absorbent hydrofiber that delivers silver</td>
</tr>
<tr>
<td>Various semipermeable membranes</td>
<td>Provide vapor and bacterial barrier</td>
</tr>
<tr>
<td>Various hydrocolloid dressings</td>
<td>Provide vapor and bacterial barrier, Absorb exudates</td>
</tr>
<tr>
<td>Various impregnated gauzes</td>
<td>Provide barrier while allowing drainage</td>
</tr>
</tbody>
</table>

![Figure 75-3 Chart to determine the developmentally related percentage of BSA affected by a burn injury. ANT, anterior; POST, posterior; R., right; L., left.](Image)
Fluid Resuscitation

Fluid resuscitation should begin soon after the injury has occurred, in the emergency department before transferring to a burn center. For most children, the Parkland formula is an appropriate starting guideline for fluid resuscitation (4 mL lactated Ringer solution/kg/% BSA burned). Half of the fluid is given over the 1st 8 hr, calculated from the time of onset of injury; the remaining fluid is given at an even rate over the next 16 hr. The rate of infusion is adjusted according to the patient’s response to therapy. Pulse and blood pressure should return to normal, and an adequate urine output (>1 mL/kg/hr in children; 0.5-1.0 mL/kg/hr in adolescents) should be accomplished by varying the IV infusion rate. Vital signs, acid–base balance, and mental status reflect the adequacy of resuscitation. Because of interstitial edema and sequestration of fluid in muscle cells, patients may gain up to 20% over baseline (preburn) body weight. Patients with burns of 30% of BSA require a large venous access (central venous line) to deliver the fluid required over the critical 1st 24 hr. Patients with burns of >60% of BSA may require a multilumen central venous catheter; these patients are best cared for in a specialized burn unit. In addition to fluid resuscitation, children should receive standard maintenance fluids (see Chapter 36).

During the 2nd 24 hr after the burn, patients begin to reabsorb edema fluid and to experience diuresis. Half of the 1st day’s fluid requirement is infused as lactated Ringer solution in 5% dextrose. Children younger than 5 yr may require the addition of 5% dextrose in the 1st 24 hr of resuscitation. Controversy exists as to whether colloid should be provided in the early period of burn resuscitation. One preference is to use colloid replacement concurrently if the burn is >85% of total BSA. Colloid is usually instituted 8-24 hr after the burn injury. In children younger than 12 mo, sodium tolerance is limited; the volume and sodium concentration of the resuscitation solution should be decreased if the urinary sodium level is rising. The adequacy of resuscitation should be constantly assessed by means of vital signs as well as urine output, blood gas, hematocrit, and serum protein measurements. Some patients require arterial and central venous lines, particularly those undergoing multiple excision and grafting procedures, as needed, for monitoring and replacement purposes. Central venous pressure monitoring may be indicated to assess circulation in patients with hemodynamic or cardiopulmonary instability. Femoral vein cannulation is a safe access for fluid resuscitation, especially in infants and children. Burn patients who require frequent blood gas monitoring benefit from radial or femoral arterial catheterization.

Oral supplementation may start as early as 48 hr after burn. Milk formula, artificial feedings, homogenized milk, or soy-based products can be given by bolus or constant infusion through a nasogastric or small bowel feeding tube. As oral fluids are tolerated, IV fluids are decreased proportionately in an effort to keep the total fluid intake constant, particularly if pulmonary dysfunction is present.

A 5% albumin infusion may be used to maintain the serum albumin levels at a desired 2 g/dL. The following rates are effective: for burns of 30-50% of total BSA, 0.3 mL of 3% albumin/kg/% BSA burn is infused over 24 hr; for burns of 50-70% of total BSA, 0.4 mL/kg/% BSA burn is infused over 24 hr; and for burns of 70-100% of total BSA, 0.5 mL/kg/% BSA burn is infused over 24 hr. Infusion of packed red blood cells is recommended if the hematocrit falls to <24% (hemoglobin = 8 g/dL). Some authorities recommend treatment for hematocrit <30% or hemoglobin <10 g/dL in patients with systemic infection, hemoglobinopathy, cardiopulmonary disease, anticipated (or ongoing) blood loss, and if repeated excision and grafting of full-thickness burns are needed. Fresh-frozen plasma is indicated if clinical and laboratory assessment shows a deficiency of clotting factors, a prothrombin level >1.5 times control, or a partial thromboplastin time >1.2 times control in children who are bleeding or are scheduled for an invasive procedure or a grafting procedure that could result in an estimated blood loss of more than half of blood volume. Fresh-frozen plasma may be used for volume resuscitation within 72 hr of injury in patients younger than 2 yr with burns over 20% of BSA and associated inhalation injury.

Sodium supplementation may be required for children with burns of >20% of BSA if 0.5% silver nitrate solution is used as the topical antibacterial burn dressing. Sodium losses with silver nitrate therapy are regularly as high as 350 mmol/m² burn surface area. Oral sodium chloride supplementation of 4 g/m² burn area/24 hr is usually well tolerated, divided into 4-6 equal doses to avoid osmotic diarrhea. The aim is to maintain serum sodium levels >130 mEq/L and urinary sodium concentration >30 mEq/L. Young children under 5 yr of age are especially susceptible to hyponatremia and cerebral edema. IV potassium supplementation is supplied to maintain a serum potassium level >3 mEq/L. Potassium losses may be significantly increased when 0.5% silver nitrate solution is used as the topical antibacterial agent or when amnoglycoside, diuretic, or amphotericin therapy is required.

Prevention of Infection and Surgical Management of the Burn Wound

Controversy exists over the prophylactic use of penicillin for all patients hospitalized with acute burn injury and the periodic replacement of central venous catheters to prevent infection. In some units, a 5-day course of penicillin therapy is used for all patients with acute burns; standard-dose crystalline penicillin is given orally or intravenously in 4 divided doses. Erythromycin may be used as an alternative in penicillin-allergic children. Other units have discontinued prophylactic use of penicillin therapy without an increase in the infection rate. Similarly, there is conflicting evidence as to whether relocation of the IV catheter every 48-72 hr decreases or increases the incidence of catheter-related sepsis. Some recommend that the central venous catheter be replaced and relocated every 5-7 days, even if the site is not inflamed and there is no suspicion of catheter-related sepsis.

Mortality related to burn injury is associated not with the toxic effect of thermally injured skin, but with the metabolic and bacterial consequences of a large open wound, reduction of the patient’s host resistance, and malnutrition. These abnormalities set the stage for life-threatening bacterial infection originating from the burn wound. Wound treatment and prevention of wound infection also promote early healing and improve aesthetic and functional outcomes. Topical treatment of the burn wound with 0.5% silver nitrate solution, silver sulfadiazine cream, or mafenide acetate (Sulfamylon) cream or topical solution at a concentration of 2.5-3% to be used for wounds with multidrug-resistant bacteria aims at prevention of infection (Table 75-6). These 3 agents have tissue-penetrating capacity. Regardless of the choice of topical antimicrobial agent, it is essential that all 3rd-degree burn tissue be fully excised before bacterial colonization occurs and that the area is grafted as early as possible to prevent deep wound sepsis. Children with a burn of >30% of BSA should be housed in a bacteria-controlled nursing unit to prevent cross-contamination.
than in adolescents and adults. Providing environmental temperatures large surface area not controlled; this is especially true in young infants, in whom the caused by cold stress if environmental humidity and temperature are 50-100% higher than predicted for their age. Early excision and grafting time lapse since the burn, children with a burn of 40% of total BSA characterized by both protein and fat catabolism. Depending on the burn injury produces a hypermetabolic response is a high priority. The burn injury produces a hypermetabolic response of 0.1-0.2 mg/kg/day given orally, to promote better protein synthesis while the nutritional support by nasogastric feeding and IV hyperalimentation continues.

**Topical Therapy**

Topical therapy is widely used and is effective against most burn wound pathogens (see Table 75-6). A number of topical agents are used: 0.5% silver nitrate solution, sulfacetamide acetate cream or solution, silver sulfdiazine cream, and Accuzyme ointment or AQUACEL Ag®. Accuzyme is an enzymatic debridement agent and may cause a stinging feeling for 15 min after application. Preferences vary among burn units. Each topical agent has advantages and disadvantages in application, comfort, and bacteriostatic spectrum. Mafenide acetate is a very effective broad-spectrum agent with the ability to diffuse through the burn eschar; it is the treatment of choice for injury to cartilaginous surface, such as the ear; mafenide acetate solution at a concentration of 5% is useful for the treatment of burn wounds that are heavily colonized with multidrug–resistant bacteria (use should be limited to 5 days). The carbonic anhydrase inhibition activity of mafenide acetate may cause acid–base imbalance if large surface areas are treated, and adverse reactions to the sulfur-containing agents may produce transient leukopenia. This latter reaction is mostly noted with the use of silver sulfadiazine cream when applied over large surface areas in children younger than 5 yr of age. This phenomenon is transient, self-limiting, and reversible. No sulfa-containing agent should be used if the child has a history of sulfa allergies.

**Nutritional Support**

Supporting the increased energy requirements of a patient with a burn is a high priority. The burn injury produces a hypermetabolic response characterized by both protein and fat catabolism. Depending on the time lapse since the burn, children with a burn of 40% of total BSA require basal energy expenditure (oxygen consumption) approximately 50-100% higher than predicted for their age. Early excision and grafting can decrease the energy requirement. Pain, anxiety, and immobilization increase the physiologic demands. Additional energy expenditure is caused by cold stress if environmental humidity and temperature are not controlled; this is especially true in young infants, in whom the large surface area:mass ratio allows proportionately greater heat loss than in adolescents and adults. Providing environmental temperatures of 28-33°C (82.4-91.4°F), adequate covering during transport and and to provide a temperature- and humidity-controlled environment to minimize hypermetabolism.

Deep 2nd-degree burns of >10% of BSA benefit from early excision and grafting. To improve outcome, sequential excision and grafting of 3rd-degree and deep 2nd-degree burns is required in children with large burns. Prompt excision with immediate wound closure is achieved with autografts, which are often meshed to increase the efficiency of coverings. Alternatives for wound closure, such as allografts, xenografts, and Integra (Integra LifeSciences, York, PA) and other synthetic skin coverings (bilaminate membrane composed of a porous lattice of crosslinked chondroitin-6-sulfate engineered to induce neovascularization as it is biodegraded), may be important for wound coverage in patients with extensive injury to limit fluid, electrolyte, and protein losses and to reduce pain and minimize temperature loss. Epidermal cultured cells (autologous keratinocytes) are a costly alternative and are not always successful. An experienced burn team can safely perform early-stage or total excision while burn fluid resuscitation continues. Important keys to success are: (1) accurate preoperative and intraoperative determination of burn depth, (2) the choice of excision area and appropriate timing, (3) control of intraoperative blood loss, (4) specific instrumentation,(5) the choice and use of perioperative antibiotics, and (6) the type of wound coverage chosen. This process can accomplish early wound coverage without the use of recombinant human growth hormone.

**Inhalational Injury**

Inhalational injury is serious in the infant and child, particularly if preexisting pulmonary conditions are present (see Chapter 71). Inhalation injury should be suspected in a patient confined to a closed space (building), with a history of an explosion or a decreased level of consciousness, or with evidence of carbon deposits in the oropharynx or nose, singed facial hair and carbonaceous sputum. Mortality estimates vary, depending on the criteria for diagnosis, but are 45-60% in adults; exact figures are not available in children. Evaluation aims at early identification of inhalation airway injuries. These may occur from (1) direct heat (greater problems with steam burns), (2) acute asphyxia, (3) carbon monoxide poisoning, and (4) toxic fumes, including cyanides from combustible plastics. Sulfur and nitrogen oxides and alkalis...
formed during the combustion of synthetic fabrics produce corrosive chemicals that may erode mucosa and cause significant tissue sloughing. Exposure to smoke may cause degradation of surfactant and decrease its production, resulting in atelectasis. Inhalation injury and burn injury are synergistic, and the combined effect can increase morbidity and mortality.

The pulmonary complications of burns and inhalation can be divided into 3 syndromes that have distinct clinical manifestations and temporal patterns:

1. Early complications include carbon monoxide poisoning, airway obstruction, and pulmonary edema. Inhalation injury should be assessed from the evidence of obvious injury (swelling or carbonaceous material in the nasal passages), wheezing, crackles or poor air entry, and laboratory determinations of (HbCO) and arterial blood gases.

   Treatment is initially focused on establishing and maintaining a patent airway through prompt and early nasotracheal or orotracheal intubation and adequate ventilation and oxygenation. Wheezing is common, and β-agonist aerosols or inhaled corticosteroids are useful. Aggressive pulmonary toilet and chest physiotherapy are necessary in patients with prolonged nasotracheal intubation or in the rare patient with a tracheotomy. An endotracheal tube can be maintained for months without the need for tracheostomy. If tracheostomy must be performed, it should be delayed until burns at and near the site have healed, and then it should be performed electively, with the child under anesthesia and the use of optimal tracheal positioning and hemostasis. In children with inhalation injury or burns of the face and neck, upper airway obstruction can develop rapidly; endotracheal intubation becomes a lifesaving intervention. Extubation should be delayed until the patient meets the accepted criteria for maintaining the airway.

   Signs of CNS injury from hypoxemia caused by asphyxia or carbon monoxide poisoning vary from irritability to depression. Carbon monoxide poisoning may be mild (<20% HbCO), with slight dyspnea, headache, nausea, and decreased visual acuity and higher cerebral functions; moderate (20-40% HbCO), with irritability, agitation, nausea, dimness of vision, impaired judgment, and rapid fatigue; or severe (40-60% HbCO), producing confusion, hallucination, ataxia, collapse, acidosis, and coma. Measurement of HbCO is important for diagnosis and treatment. The PaO2 value may be normal and the HbCO saturation values misleading because HbCO is not detected by the usual tests of oxygen saturation. Carbon monoxide poisoning is assumed until the tests are performed, and it is treated with 100% oxygen. Significant carbon monoxide poisoning requires hyperbaric oxygen therapy (see Chapter 63).

   Patients with severe inhalation injury or with other causes of respiratory deterioration that lead to acute respiratory distress syndrome who do not improve with conventional pressure-controlled ventilation (progressive oxygenation failure, as manifested by oxygen saturation <90% while receiving FIO2 of 0.9-1.0 and positive end-expiratory pressure of at least 12.5 cm H2O) may benefit from high-frequency ventilation or nitric oxide inhalation treatment. Nitric oxide usually is administered through the ventilator at 5 parts per million (ppm) and increased to 30 ppm. This method of therapy reduces the need for extracorporeal membrane oxygenation.

**Pain Relief and Psychologic Adjustment**

See Chapter 62.

It is important to provide adequate analgesia, anxiolytics, and psychologic support to reduce early metabolic stress, decrease the potential for posttraumatic stress syndrome, and allow future stabilization as well as physical and psychologic rehabilitation. Patients and family members require team support to work through the grieving process and accept long-term changes in appearance.

Children with burn injury show frequent and wide fluctuations in pain intensity. Appreciation of pain depends on the depth of the burn; the stage of healing; the patient’s age and stage of emotional development and cognition; the experience and efficiency of the treating team; the use of analgesics and other drugs; the patient’s pain threshold; and interpersonal and cultural factors. From the onset of treatment, preemptive pain control during dressing changes is of paramount importance. The use of a variety of nonpharmacologic interventions as well as pharmacologic agents must be reviewed throughout the treatment period. Opiate analgesia, prescribed in an adequate dose and timed to cover dressing changes, is essential to comfort management. A supportive person who is consistently present and “knows” the patient profile can integrate and encourage patient participation in burn care. The problem of undermedication is most prevalent in adolescents, in whom fear of drug dependence may inappropriately influence treatment. A related problem is that the child’s specific pain experience may be misinterpreted; for anxious patients, those who are confused and alone, or those with preexisting emotional disorders, even small wounds may illicit intense pain. Anxiolytic medication added to the analgesic is usually helpful and has more than a synergistic effect. Equal attention is necessary to decrease stress in the intubated patient. Other modalities of pain and anxiety relief (relaxation techniques) can decrease the physiologic stress response. Oral morphine sulfate (immediate release) is recommended at a consistent schedule at a dose of 0.3-0.6 mg/kg every 4-6 hr initially and until wound cover is accomplished. Morphine sulfate IV bolus at a dose of 0.05-0.1 mg/kg maximum of 2.5 mg every 2 hr is administered. Morphine sulfate rectal suppositories may be useful at a dose of 0.3-0.6 mg/kg every 4 hr when oral administration is not possible. The use of codeine preparation should be limited to children older than age 6 yr because of the “ultrapapid metabolizers” of codeine into morphine. For anxiety, lorazepam is given on a consistent schedule, 0.05-0.1 mg/kg/dose every 6-8 hr. To control pain during a procedure (dressing change or debride-ment), oral morphine at a dose of 0.3-0.6 mg/kg is given 1-2 hr before the procedure and this is supplemented by a morphine IV bolus at a dose of 0.05-0.1 mg/kg given immediately before the procedure. Lorazepam at a dose of 0.04 mg/kg is given orally or intravenously, if necessary, for anxiety before the procedure. Midazolam (Versed) is also very useful for conscious sedation given at a dose of 0.01-0.02 mg/kg for nonintubated patients and 0.05-0.1 mg/kg for intubated patients, as an intravenous infusion or bolus, and may be repeated in 10 min. During the process of weaning from analgesics, the dose of oral opiates is reduced by 25% over 1-3 days, sometimes with the addition of acetaminophen as opiates are tapered. Antianxiety medications are tapered by reducing the dose of benzo diazepines at 25-50% per dose daily over 1-3 days.

For ventilated patients, pain control is accomplished by using morphine sulfate intermittently as an IV bolus at a dose of 0.05-0.1 mg/kg every 2 hr. Doses may need to be increased gradually, and some children may need continuous infusion; a starting dose of 0.05 mg/kg/hr given as an infusion is increased gradually as the need of the child changes. Naloxone is rarely needed but should be immediately available to reverse the effect of morphine, if necessary; if needed for an airway crisis, it should be given in a dose of 0.1 mg/kg up to a total of 2 mg, either intramuscularly or intravenously. For patients undergoing assisted respiration who require treatment of anxiety, midazolam is used as an intermittent IV bolus (0.04 mg/kg given by slow push every 4-6 hr) or as a continuous infusion. For intubated patients, opiates do not need to be discontinued during the process of weaning from the ventilator. Benzodiazepine should be reduced to approximately half the dose over 24-72 hr before extubation; too-rapid weaning from a benzodiazepine can lead to seizures.

There is a growing use of psychotropic medication in the care of children with burns, including prescription of selective serotonin reuptake inhibitors as antidepressants, the use of haloperidol as a neuroleptic in the critical care setting, and the treatment of post-traumatic stress disorder with benzodiazepines. Conscious sedation utilizing ketamine or propofol may be used for major dressing changes.
Reconstruction and Rehabilitation
To ensure maximum cosmetic and functional outcome, occupational and physical therapy must begin on the day of admission, continue throughout hospitalization, and, for some patients, continue after discharge. Physical rehabilitation involves body and limb positioning, splinting, exercises (active and passive movement), assistance with activities of daily living, and gradual ambulation. These measures maintain adequate joint and muscle activity with as normal a range of movement as possible after healing or reconstruction. Pressure therapy is necessary to reduce hypertrophic scar formation; a variety of prefabricated and custom-made garments are available for use in different body areas for prevention of hypertrophic scarring. These custom-made garments deliver consistent pressure on scarred areas; they shorten the time of scar maturation and decrease the thickness of the scar, the redness, and the associated itching. Continued adjustments to scarred areas (scar release, grafting, rearrangement) and multiple minor cosmetic surgical procedures are necessary to optimize long-term function and improve appearance. Replacement of areas of alopecia and scarring has been achieved with the use of tissue expander techniques. The use of ultrapulse laser for reduction of scarring is an adjunct in scar management.

School Reentry and Long-Term Outcome
It is best for the child to return to school immediately after discharge. Occasionally, a child may need to attend a few half-days (because of rehabilitation needs). It is important for the child to return to the child’s normal routine of attending school and being with peers. Planning for a return to home and school often requires a school reentry program that is individualized to each child’s needs. For a school-age child, planning for the return to school occurs simultaneously with planning for discharge. The hospital schoolteacher contacts the local school and plans the program with the school faculty, nurses, social workers, recreational/child-life therapists, and rehabilitation therapists. This team should work with students and staff to ease anxiety, answer questions, and provide information. Burns and scars evoke fears in those who are not familiar with this type of injury and can result in a tendency to withdraw from or reject the burned child. A school reentry program should be appropriate to a child’s development and changing educational needs.

Major advances have made it possible to save the lives of children with massive burns; whereas some children have had lingering physical difficulties, most have a satisfactory quality of life. The comprehensive burn care that includes experienced multidisciplinary aftercare plays an important role in recovery. Table 75-7 lists the long-term complications of burns.

**SPECIAL SITUATIONS**

**Electrical Burns**
There are 3 types of electrical burns. Minor electrical burns usually occur as a result of hitting on an extension cord. These injuries produce localized burns to the mouth, which usually involve the portions of the upper and lower lips that come in contact with the extension cord. The injury may involve or spare the corners of the mouth. Because these are nonconductive injuries (do not extend beyond the site of injury), hospital admission is not necessary and care is focused on the area of the injury visible in the mouth, it is low voltage, does not cause entry or exit wounds, or cardiac issues. Treatment with topical antibiotic creams is sufficient until the patient is seen in a burn unit outpatient department or by a plastic surgeon.

A more serious category of electrical burn is the high-tension electrical wire burn, for which children must be admitted for observation, regardless of the extent of the surface area burn. Deep muscle injury is typical and cannot be readily assessed initially. These injuries result from high voltage (>1,000 V) and occur particularly at high-voltage installations, such as electric power stations or railroads; children climb an electric pole and touch an electric box out of curiosity or accidentally touch a high-tension electric wire. Such injuries have a mortality rate of 3-15% for children who arrive at the hospital for treatment. Survivors have a high rate of morbidity, including major limb amputations. Points of entry of current through the skin and the exit site show characteristic features consistent with current density and heat. The majority of entrance wounds involve the upper extremity, with small exit wounds in the lower extremity. The electrical path, from entrance to exit, takes the shortest distance between the 2 points and may produce injury in any organ or tissue in the path of the current. Multiple exit wounds in some patients attest to the possibility of several electrical pathways in the body, placing virtually any structure in the body at risk (Table 75-8). Damage to the abdominal viscera, thoracic structures, and the nervous system (confusion, coma, paralysis) in areas remote from obvious extremity injury occurs and must be sought, particularly in injuries with multiple current pathways or those in which the victim falls from a high pole. Sometimes an ignition occurs and results in concurrent flame burn and clothing fire. Cardiac abnormalities, manifested as ventricular fibrillation or cardiac arrest, are common; patients with high-tension electrical injury need an initial electrocardiogram and cardiac monitoring until they are stable and have been fully assessed. Higher-risk patients have abnormal electrocardiographic findings and a history of loss of consciousness. Renal damage from deep muscle necrosis and subsequent myoglobinuria is another complication; such patients need forced alkaline diuresis to minimize renal damage. Soft-tissue (muscle) injury of an extremity may produce a compartment syndrome. Aggressive removal of all dead

<table>
<thead>
<tr>
<th>Table 75-7 Common Long-Term Disabilities in Patients with Burn Injuries</th>
</tr>
</thead>
<tbody>
<tr>
<td>DISABILITIES AFFECTING THE SKIN AND SOFT TISSUE</td>
</tr>
<tr>
<td>Hypertrophic scars</td>
</tr>
<tr>
<td>Susceptibility to minor trauma</td>
</tr>
<tr>
<td>Dry skin</td>
</tr>
<tr>
<td>Contractures</td>
</tr>
<tr>
<td>Itching and neuropathic pain</td>
</tr>
<tr>
<td>Alopecia</td>
</tr>
<tr>
<td>Chronic open wounds</td>
</tr>
<tr>
<td>Skin cancers</td>
</tr>
<tr>
<td>ORTHOPEDIC DISABILITIES</td>
</tr>
<tr>
<td>Amputations</td>
</tr>
<tr>
<td>Contractures</td>
</tr>
<tr>
<td>Heterotopic ossification</td>
</tr>
<tr>
<td>Temporary reduction in bone density</td>
</tr>
<tr>
<td>METABOLIC DISABILITIES</td>
</tr>
<tr>
<td>Heat sensitivity</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>PSYCHIATRIC AND NEUROLOGIC DISABILITIES</td>
</tr>
<tr>
<td>Sleep disorders</td>
</tr>
<tr>
<td>Adjustment disorders</td>
</tr>
<tr>
<td>Posttraumatic stress syndrome</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>Body image issues</td>
</tr>
<tr>
<td>Neuropathy and neuropathic pain</td>
</tr>
<tr>
<td>Long-term neurologic effects of carbon monoxide poisoning</td>
</tr>
<tr>
<td>Anoxic brain injury</td>
</tr>
<tr>
<td>LONG-TERM COMPLICATIONS OF CRITICAL CARE</td>
</tr>
<tr>
<td>Deep-vein thrombosis, venous insufficiency, or varicose veins</td>
</tr>
<tr>
<td>Tracheal stenosis, vocal cord disorders, or swallowing disorders</td>
</tr>
<tr>
<td>Renal or adrenal dysfunction</td>
</tr>
<tr>
<td>Hepatobiliary or pancreatic disease</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>Reactive airway disease or bronchial polyposis</td>
</tr>
<tr>
<td>PREEXISTING DISABILITIES THAT CONTRIBUTED TO THE INJURIES</td>
</tr>
<tr>
<td>Risk-taking behavior</td>
</tr>
<tr>
<td>Untreated or poorly treated psychiatric disorder</td>
</tr>
</tbody>
</table>

Table 75-8  Electrical Injury: Clinical Considerations

<table>
<thead>
<tr>
<th>CLINICAL MANIFESTATIONS</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Extricate the patient; perform ABCs of resuscitation; immobilize the spine.</td>
</tr>
<tr>
<td></td>
<td>History: voltage, type of current</td>
</tr>
<tr>
<td></td>
<td>Complete blood count with platelets, electrolytes, blood urea nitrogen (BUN), creatinine, glucose</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Treat dysrhythmias</td>
</tr>
<tr>
<td></td>
<td>Cardiac monitor, electrocardiogram, and radiographs with suspected thoracic injury</td>
</tr>
<tr>
<td></td>
<td>Creatinine phosphokinase with isoenzyme measurements if indicated</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Protect and maintain the airway</td>
</tr>
<tr>
<td></td>
<td>Mechanical ventilation if indicated, chest radiograph, arterial blood gas levels</td>
</tr>
<tr>
<td>Renal</td>
<td>Provide aggressive fluid management unless a central nervous system injury is present</td>
</tr>
<tr>
<td></td>
<td>Maintain adequate urine output, &gt;1 mL/kg/hr</td>
</tr>
<tr>
<td></td>
<td>Consider central venous or pulmonary artery pressure monitoring</td>
</tr>
<tr>
<td></td>
<td>Measure urine myoglobin; perform urinalysis; measure BUN, creatinine</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Treat seizures</td>
</tr>
<tr>
<td></td>
<td>Provide fluid restriction if indicated</td>
</tr>
<tr>
<td></td>
<td>Consider spine radiographs, especially cervical</td>
</tr>
<tr>
<td>Cutaneous/oral</td>
<td>Search for the entrance/exit wound</td>
</tr>
<tr>
<td></td>
<td>Treat cutaneous burns; determine the tetanus status</td>
</tr>
<tr>
<td></td>
<td>Obtain a plastic surgery of ear, nose, and throat consultation if needed</td>
</tr>
<tr>
<td></td>
<td>No entry or exit wounds, no cardiac involvement. All injuries are localized management is observation till eschar slough off and granulation tissue fills in. Obtain plastic surgeon evaluation after first healing had occurred usually with scar formation.</td>
</tr>
<tr>
<td>Abdominal</td>
<td>Place a nasogastric tube if the patient has airway compromise or ileus</td>
</tr>
<tr>
<td></td>
<td>Obtain serum glutamate oxaloacetate transaminase or aspartate aminotransferase, serum glutamate-pyruvic transaminase, alanine aminotransferase, amylase, BUN, and creatinine measurements and, CT scans as indicated</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Monitor the patient for possible compartment syndrome</td>
</tr>
<tr>
<td></td>
<td>Obtain radiographs and orthopedic/general surgery consultations as indicated</td>
</tr>
<tr>
<td>Ocular</td>
<td>Obtain an ophthalmology consultation as indicated</td>
</tr>
</tbody>
</table>


and devitalized tissue, even with the risk of functional loss, remains the key to effective management of the electrically damaged extremity. Early debridement facilitates early closure of the wound. Damaged major vessels must be isolated and buried in a viable muscle to prevent exposure. Survival depends on immediate intensive care, whereas a functional result depends on long-term care and delayed reconstructive surgery.

Lightning burns occur when a high-voltage current directly strikes a person (most dangerous) or when the current strikes the ground or an adjacent (in-contact) object. A step voltage burn is observed when lightning strikes the ground and travels up one leg and down the other (the path of least resistance). Lightning burns depend on the current path, the type of clothing worn, the presence of metal, and cutaneous moisture. Entry, exit, and path lesions are possible; the prognosis is poorest for lesions of the head or legs. Internal organ injury along the path is common and does not relate to the severity of the cutaneous burn. Linear burns, usually 1st- or 2nd-degree, are in the locations where sweat is present. Feathering or an arborescent pattern is characteristic of lightning injury. Lightning may ignite clothing or produce serious cutaneous burns from heated metal in the clothing. Internal complications of lightning burns include cardiac arrest caused by asystole, transient hypertension, premature ventricular contractions, ventricular fibrillation, and myocardial ischemia. Most severe cardiac complications resolve if the patient is supported with cardiopulmonary resuscitation (see Chapter 67). CNS complications include cerebral edema, hemorrhage, seizures, mood changes, depression, and paralysis of the lower extremities. Rhabdomyolysis and myoglobinuria (with possible renal failure) also occur. Ocular manifestations include vitreous hemorrhage, iridocyclitis, retinal tearing or retinal detachment.

Bibliography is available at Expert Consult.
Bibliography


Useful Links

www.ameriburn.org.
www.cpsc.gov.
www.safekids.org.
The involvement of children and youth in snowmobiling, mountain climbing, winter hiking, and skiing places them at risk for cold injury. Cold injury may produce either local tissue damage, with the injury pattern depending on exposure to damp cold (frostnip, immersion foot, or trench foot), dry cold (which leads to local frostbite), or generalized systemic effects (hypothermia).

**PATHOPHYSIOLOGY**

Ice crystals may form between or within cells, interfering with the sodium pump, and may lead to rupture of cell membranes. Further damage may result from clumping of red blood cells or platelets, causing microembolism or thrombosis. Blood may be shunted away from an affected area by secondary neurovascular responses to the cold injury; this shunting often further damages an injured part while improving perfusion of other tissues. The spectrum of injury ranges from mild to severe and reflects the result of structural and functional disturbance in small blood vessels, nerves, and skin.

**ETIOLOGY**

Body heat may be lost by conduction (wet clothing, contact with metal or other solid conducting objects), convection (wind chill), evaporation, or radiation. Susceptibility to cold injury may be increased by dehydration, alcohol or drug use, impaired consciousness, exhaustion, hunger, anemia, impaired circulation as a consequence of cardiovascular disease, and sepsis; it is also greater in very young or older persons. Certain medications may contribute to hypothermia, while others may display reduced metabolism or clearance during hypothermia (Table 76-1).

Hypothermia occurs when the body can no longer sustain normal core temperature by physiologic mechanisms, such as vasocostriction, shivering, muscle contraction, and nonshivering thermogenesis. When shivering ceases, the body is unable to maintain its core temperature; when the body core temperature falls to <35°C (95°F), the syndrome of hypothermia occurs. Wind chill, wet or inadequate clothing, and other factors increase local injury and may cause dangerous hypothermia, even in the presence of an ambient temperature that is not <17-20°C (50-60°F).

**CLINICAL MANIFESTATIONS**

**Frostnip**

Frostnip results in the presence of firm, cold, white areas on the face, ears, or extremities. Blistering and peeling may occur over the next 24-72 hr, occasionally leaving mildly increased hypersensitivity to cold for some days or weeks. Treatment consists of warming the area with an unaffected hand or a warm object before the lesion reaches a stage for some days or weeks. Treatment consists of warming the damaged area. It is important not to cause further damage by attempting to rub the area with ice or snow. The area may be warmed against an unaffected hand, the abdomen, or an axilla during transfer of the patient to a facility where more rapid warming with a warm (not hot) water bath is possible. If the skin becomes painful and swelling occurs, antiinflammatory agents are helpful and an analgesic agent is necessary. Freeze and rethaw cycles are most likely to cause permanent tissue injury, and it may be necessary to delay definitive warming and apply only mild measures if the patient is required to walk on the damaged feet en route to definitive treatment. In the hospital, the affected area should be immersed in warm water (approximately 42°C [107.6°F]), with care taken not to burn the anesthetized skin. Broken vesicles may be debrided, but intact vesicles should be left alone. Vasodilating agents, such as prazosin and phenoxybenzamine, may be helpful. Use of anticoagulants (heparin, dextran) has had equivocal results; results of chemical and surgical sympathectomy have also been equivocal. Oxygen is of help only at high altitudes. Meticulous local care, prevention of infection, and keeping the rewarmed area dry, open, and sterile provide optimal results. Recovery can be complete, and prolonged observation with conservative therapy is justified before any excision or amputation of tissue is considered. Analgesia and maintenance of good nutrition are necessary throughout the prolonged waiting period.

**Immersion Foot (Trench Foot)**

Immersion foot occurs in cold weather when the feet remain in damp or wet, poorly ventilated boots. The feet become cold, numb, pale, edematous, and clammy. Tissue maceration and infection are likely, and prolonged autonomic disturbance is common. This autonomic disturbance leads to increased sweating, pain, and hypersensitivity to temperature changes, which may persist for years. Treatment includes drying the foot, gentle rewarming and nonsteroidal antiinflammatory drugs for pain. Prevention consists of using well-fitting, insulated, waterproof, nonconstricting footwear. Once damage has occurred, patients must choose clothing and footwear that are more appropriate, dry, and well-fitting. The disturbance in skin integrity is managed by keeping the affected area dry and well-ventilated and by preventing or treating infection. Only supportive measures are possible for control of autonomic symptoms.

**Frostbite**

With frostbite, initial stinging or aching of the skin progresses to cold, hard, white anesthetic and numb areas. Clear or hemorrhagic vesicles may develop over the exposed areas. On rewarming, the area becomes blotchy, itchy, and often red, swollen, and painful. The injury spectrum ranges from complete normality to extensive tissue damage, even gangrene, if early relief is not obtained.

Treatment consists of warming the damaged area. It is important not to cause further damage by attempting to rub the area with ice or snow. The area may be warmed against an unaffected hand, the abdomen, or an axilla during transfer of the patient to a facility where more rapid warming with a warm (not hot) water bath is possible. If the skin becomes painful and swelling occurs, antiinflammatory agents are helpful and an analgesic agent is necessary. Freeze and rethaw cycles are most likely to cause permanent tissue injury, and it may be necessary to delay definitive warming and apply only mild measures if the patient is required to walk on the damaged feet en route to definitive treatment. In the hospital, the affected area should be immersed in warm water (approximately 42°C [107.6°F]), with care taken not to burn the anesthetized skin. Broken vesicles may be debrided, but intact vesicles should be left alone. Vasodilating agents, such as prazosin and phenoxybenzamine, may be helpful. Use of anticoagulants (heparin, dextran) has had equivocal results; results of chemical and surgical sympathectomy have also been equivocal. Oxygen is of help only at high altitudes. Meticulous local care, prevention of infection, and keeping the rewarmed area dry, open, and sterile provide optimal results. Recovery can be complete, and prolonged observation with conservative therapy is justified before any excision or amputation of tissue is considered. Analgesia and maintenance of good nutrition are necessary throughout the prolonged waiting period.

**Hypothermia**

Hypothermia may occur in winter sports when injury, equipment failure, or exhaustion decreases the level of exertion, particularly if sufficient attention is not paid to wind chill. Immersion in frozen bodies of water and wet wind chill rapidly produce hypothermia. As the core temperature of the body falls, insidious onset of extreme lethargy, fatigue, incoordination, and apathy occurs, followed by mental confusion, clumsiness, irritability, hallucinations, and finally, bradycardia. A number of medical conditions, such as cardiac disease, diabetes mellitus, hypoglycemia, sepsis, β-blocking agent overdose, and substance abuse, may need to be considered in a differential diagnosis. The decrease in rectal temperature to <34°C (93°F) is the most helpful diagnostic feature. Hypothermia associated with drowning is discussed in Chapter 74.

Prevention is a high priority. Of extreme importance for those who participate in winter sports is wearing layers of warm clothing, gloves, socks within insulated boots that do not impede circulation, and a warm head covering, as well as application of adequate waterproofing and protection against the wind. Thirty percent of heat loss for infants occurs from the head. Ample food and fluid must be provided during exercise. Those who participate in sports should be alert to the presence of cold or numbing of body parts, particularly the nose, ears, and

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**Table 76-1**

<table>
<thead>
<tr>
<th>Drugs Displaying Reduced Metabolism or Clearance in Hypothermia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine, Digoxin, Fentanyl, Gentamicin, Lidocaine, Phentobarbital</td>
</tr>
</tbody>
</table>

*Modified from Bope ET, Kellerman RD, editors, Conn’s current therapy 2014, Philadelphia, 2014, Elsevier/Saunders, Box 3, p. 1135*
extremities, and they should review methods to produce local warming and know to seek shelter if they detect symptoms of local cold injury. Application of petrolatum (Vaseline) to the nose and ears gives certain protection against frostbite.

Treatment at the scene aims at prevention of further heat loss and early transport to adequate shelter (Table 76-2). Dry clothing should be provided as soon as practical, and transport should be undertaken if the victim has a pulse. If no pulse is detected at the initial review, cardiopulmonary resuscitation is indicated (see Chapter 67; Fig. 76-1). During transfer, jarring and sudden motion should be avoided because these occurrences may cause ventricular arrhythmia. It is often difficult to attain a normal sinus rhythm during hypothermia.

If the patient is conscious, mild muscle activity should be encouraged, and a warm drink offered. If the patient is unconscious, external warming should be undertaken initially with use of blankets and a sleeping bag; wrapping the patient in blankets or sleeping bag with a warm companion may increase the efficiency of warming. On arrival at a treatment center while a warming bath of 45–48°C (113–118°F) water is prepared, the patient should be warmed through inhalation of warm, moist air or oxygen or with heating pads or thermal blankets. Monitoring of serum chemistry values and an electrocardiogram are

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**Figure 76-1** Recommendations for out-of-hospital evaluation and treatment of accidental hypothermia. ECG, electrocardiogram; CPR, cardiopulmonary resuscitation; HPMK, Hypothermia Prevention Management Kit; IV, intravenous; IO, intraosseous; ETCO2, end-tidal carbon dioxide; VT, ventricular tachycardia; VF, ventricular fibrillation; AED, automatic external defibrillator; US, ultrasound; ICU, intensive care unit; ECC, extracorporeal circulation. (From Zafren K, Giesbrecht GG, Danzl DF, et al: Wilderness Medical Society Practice Guidelines for the Out-of-Hospital Evaluation and Treatment of Accidental Hypothermia: 2014 Update, Wilderness Environ Med 25:S66–S85, 2014. Fig 2.)
necessary until the core temperature rises to >35°C (95°F) and can be stabilized. Control of fluid balance, pH, blood pressure, and oxygen concentration is necessary in the early phases of the warming period and resuscitation. In severe hypothermia, there may be a combined respiratory and metabolic acidosis. Hypothermia may falsely elevate pH; nonetheless, most authorities recommend warming the arterial blood gas specimen to 37°C (98.6°F) before analysis and regarding the result as one from a normothermic patient. In patients with marked abnormalities, warming measures, such as gastric or colonic irrigation with warm saline or peritoneal dialysis, may be considered, but the effectiveness of these measures in treating hypothermia is unknown. In accidental deep hypothermia (core temperature 28°C [82.4°F]) with circulatory arrest, rewarming with cardiopulmonary bypass may be lifesaving for previously healthy young individuals. If rewarming is not successful despite appropriate measures, one should suspect infection, drug overdose, endocrine disorders, or a futile resuscitation.

Chilblain (Pernio)
Chilblain (pernio) is a form of cold injury in which erythematous, vesicular, or ulcerative lesions occur. The lesions are presumed to be of vascular or vasoconstrictive origin. They are often itchy, may be painful, and result in swelling and scabbing. The lesions are most often found on the ears, the tips of the fingers and toes, and exposed areas of the legs. The lesions last for 1-2 wk but may persist for longer. Treatment consists of prophylaxis: avoiding prolonged chilling and protecting potentially susceptible areas with a cap, gloves, and stockings. Prazosin and phenoxybenzamine may be helpful in improving circulation if this is a recurrent problem. For significant itching, local corticosteroid preparations may be helpful.

COLD-INDUCED FAT NECROSIS (PANNICULITIS)
A common, usually benign injury, cold-induced fat necrosis occurs upon exposure to cold air, snow, or ice and manifests in exposed (or, less often, covered) surfaces as red (or, less often, purple to blue) macular, papular, or nodular lesions. Treatment is with nonsteroidal antiinflammatory agents. The lesions may last 10 days to 3 wk (see Chapter 660) but may persist for longer. There is a possibility of severe coagulopathy associated with poor outcome in some of the severe cold injuries, thus meriting anticoagulation therapy.

Bibliography is available at Expert Consult.
Bibliography


Genetic testing involves analyzing genetic material to obtain information related to a person's health status using chromosomal (cytogenetic) analysis (see Chapter 81) or DNA-based testing.

**DIAGNOSTIC TESTING**

Diagnostic genetic testing helps explain a set of signs and/or symptoms of a disease. The list of disorders for which specific genetic tests is available is extensive. The website http://www.ncbi.nlm.nih.gov/gtr/ provides a database of available tests that is provider driven and so claims are not validated by the site's host, the National Institutes of Health.

Single-gene disorders can be tested by at least 3 different approaches: linkage analysis, array comparative genomic hybridization (aCGH), and direct mutation (DNA sequence-based) analysis, usually by DNA sequencing (Table 77-1). Linkage analysis is used if the responsible gene is mapped but not yet identified, or if it is impractical to find specific mutations, usually because of the large size and larger number of different mutations in some genes. aCGH can be used to detect large multigene deletions or duplications (copy number variations). In addition, with increasing resolution, single gene or smaller intragenic deletions or duplications can be detected by aCGH. *Direct DNA mutation analysis* is preferred and is possible with the availability of the complete human genome sequence. An emerging feature is the increasing recognition of oligogenic disease where more than 1 disease gene contributes to a complex phenotype. The ability to sequence hundreds to thousands of genes at once has provided insight into this added layer of complexity in disease pathogenesis.

**Linkage testing** involves tracking a genetic trait through a family using closely linked polymorphic markers as a surrogate for the trait (Fig. 77-1). It requires testing an extended family and is vulnerable to several pitfalls, such as genetic recombination, genetic heterogeneity, and incorrect diagnosis in the proband. Genetic recombination occurs between any pair of loci, the frequency being proportional to the distance between them. This problem can be ameliorated by using very closely linked markers and, if possible, using markers that flank the specific gene. Genetic heterogeneity can be problematic for a linkage-based test if there are multiple distinct genomic loci that can cause the same phenotype, resulting in the risk that the locus tested for is not the one responsible for disease in the family. Incorrect diagnosis in the proband also leads to tracking the wrong gene. Linkage testing remains useful for several genetic conditions, though it is increasingly being superseded by the availability of direct DNA sequencing. It is critically important that genetic counseling be provided to the family to explain the complexities of interpretation of test results.

aCGH (see Chapter 81) can detect copy number variation in a patient's DNA by comparing it to a standard control DNA. In so doing, it provides a level of genetic resolution between what is available with DNA sequencing and what is available with chromosome analysis. Whereas earlier technologies could only identify large deletions or duplications that might encompass multiple genes, aCGH can resolve deletions or duplications of several kilobases within 1 gene. In theory, this approach can detect deletion and duplication mutations that would be missed by either chromosome analysis or direct mutation testing by DNA sequencing. However, because the specific resolution and coverage of different aCGH platforms can vary tremendously for different gene regions, the sensitivity for detecting deletions and duplications can vary for different diseases and laboratories.

**Direct DNA-based mutation testing** avoids the pitfalls of linkage testing by detecting the specific gene mutation (i.e., sequence change). The specific approach used is customized to the biology of the gene being tested. In some disorders, 1 or a few distinct mutations occur in all affected individuals. This is the case in sickle cell anemia, in which the same single base substitution occurs in everyone with the disorder. In other conditions, there may be many possible mutations that account for the disorder in different individuals. Cystic fibrosis is an example: more than 1,000 distinct mutations have been found in the CFTR gene. Mutation analysis is challenging because no single technique can detect all possible mutations. However, with the completion of the human genome sequence and high-throughput DNA sequencing technology, the approach of choice is to directly sequence DNA that is generated by polymerase chain reaction (PCR) amplification of DNA isolated from peripheral blood white blood cells. The limitation of this approach is that only DNA that is amplified is sequenced, and usually this is restricted to the coding or exonic regions of a gene. Because mutations sometimes occur in the noncoding intronic regions, failure to detect a mutation does not exclude the diagnosis. In addition, genes in a deleted region will not be deleted. Although DNA sequencing can be highly specific, it is not completely sensitive because of practical limitations of what is commercially available. This is, however, rapidly changing because of technologic advances.

The most useful development in clinical DNA diagnosis is application of *next-generation sequencing* technology to testing panels of genes that target disease symptoms (e.g., low bone mass, ataxia) or the whole exome (whole exome sequencing [WES]). Here, advances in sequencing methodology have allowed for massively parallel sequencing of hundreds of genes of all of the gene coding sequences (approximately 20,000 genes) from single sample. The challenge is not so much the generation of DNA sequence, but the interpretation of enormous genetic variation within a single sample. Direct sequencing of tens to hundreds of genes in next generation sequencing panels offer a potentially higher sensitivity as the “depth” of read is higher without complicating high discovery rate of variants of unknown sequences (VUS). WES also offers the potential for identifying new disease-gene associations as well as phenotypes caused by more than one disease gene (i.e., oligogenic phenotypes). An important ethical consideration is the reporting of incidental findings, whether medically or nonmedically actionable in a patient; WES may identify mutations that cause aminoglycoside sensitive hearing loss. This would be medically actionable. At the same time, the discovery of apolipoprotein E variants in a child that increase Alzheimer disease risk susceptibility may not. Hence, counseling for patients undergoing WES is important so that only wanted results are reported back to the patient. Guidelines are currently evolving for reporting of incidental findings for WES by the American College of Medical Genetics (www.acmg.net). Practice varies among institutions and recommendations vary among international genetic organizations about the approach for revealing incidental findings to patients. Many leave the choice up to the patient/family about revealing incidental findings from WES/whole genome sequencing. Most require revealing to the patient/family significant diseases
Variants That Are Incidental Findings Are Approaches for Genetic Testing

recessive

repeated, because it is assumed that the result will not change over possible, and unlike most medical tests, a genetic test is unlikely to be human error, such as sample mix-up, has not occurred. Such errors are Most genetic tests have a very high analytical validity, assuming that

Does the test correctly detect the presence or absence of mutation?

Table 77-1 Approaches for Genetic Testing

<table>
<thead>
<tr>
<th>TYPE OF MUTATION TESTING</th>
<th>RESOLUTION</th>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
<th>SAMPLE REQUIREMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linkage</td>
<td>Depends on location of polymorphic markers near putative disease gene</td>
<td>Possible when specific disease-causing genetic mutation is not identifiable or found</td>
<td>Can give only diagnostic probability based on likelihood of genetic recombination between presumed DNA mutation and polymorphic markers</td>
<td>Requires multiple family members with documented mendelian pattern of inheritance within family</td>
</tr>
<tr>
<td>aCGH</td>
<td>Several kilobases to several hundreds of kilobases</td>
<td>Able to detect small deletion or duplications within 1 or more genes</td>
<td>Can miss small deletions or insertions depending on resolution of the array used</td>
<td>Single patient sample sufficient, though having sample from biological parents can help with interpretation</td>
</tr>
<tr>
<td>Direct DNA-based testing (e.g., DNA sequencing)</td>
<td>Single base-pair changes</td>
<td>High specificity if previously described deleterious mutation is found</td>
<td>Can miss deletion or duplication of a segment of gene</td>
<td>Single patient sample sufficient, though having sample from biological parents can help with interpretation</td>
</tr>
</tbody>
</table>

Figure 77-1 Use of linkage analysis in prenatal diagnosis of an autosomal recessive disorder. Both parents are carriers, and they have 1 affected son. The numbers below the symbols indicate alleles at 3 polymorphic loci: A, B, and C. Locus B resides within the disease gene. The affected son inherited the 1-2-2 chromosome from his father and the 2-1-2 chromosome from his mother. The fetus has inherited the same chromosome from the father, but the 3-2-4 chromosome from the mother and therefore is most likely to be a carrier.

Table 77-2 Variants That Are Incidental Findings Are Assigned to 1 of 4 Categories

<table>
<thead>
<tr>
<th>Disease gene</th>
<th>A 2 1</th>
<th>B 3 2</th>
<th>C 1 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>C 1 2</td>
<td>1 2</td>
<td>2 1</td>
<td>2 2</td>
</tr>
<tr>
<td>fetus</td>
<td>3 2</td>
<td>2 1</td>
<td>4 2</td>
</tr>
</tbody>
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Pathogenicity. These include finding the variant only in affected individuals, inferring that the variant alters the function of the gene product, determining whether the amino acid altered by the mutation is conserved in evolution, and determining whether the mutation segregates with disease in the family. In some cases, it is possible to be sure whether the variant is pathogenic or incidental. In spite of all of these approaches, it might still be impossible to definitively assign causality with 100% confidence.

False-negative results reflect an inability to detect a mutation in an affected patient. This occurs principally in disorders where genetic heterogeneity—allellic (different mutations occur in one causative gene) heterogeneity or locus (more than one gene can cause a disease) heterogeneity—is the rule. It is difficult to detect all possible mutations within a gene, because mutations can be varied in location within the gene and in the type of mutation. Direct sequencing may miss gene deletions or rearrangements, and mutations may be found within non-coding sequences such as introns or the promoter; a negative DNA test does not necessarily exclude a diagnosis.

Clinical validity is the degree to which the test correctly predicts presence or absence of disease. False-positive and false-negative test results can occur. False-positive results are more likely for predictive tests than for diagnostic tests. An important contributing factor is nonpenetrance: An individual with an at-risk genotype might not clinically express the condition. Another factor is the finding of a genetic variant of unknown significance. Detection of a base sequence variation in an affected patient does not prove that it is the cause of the patient’s disorder. In exomic sequencing, there may be more than 30,000 VUS; in whole genome sequencing there may be more than 3,000,000 VUS. Various lines of evidence are used to establish pathogenicity. These include finding the variant only in affected individuals, inferring that the variant alters the function of the gene product, determining whether the amino acid altered by the mutation is conserved in evolution, and determining whether the mutation segregates with disease in the family. In some cases, it is possible to be sure whether the variant is pathogenic or incidental. In spite of all of these approaches, it might still be impossible to definitively assign causality with 100% confidence.

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Clinical validity is the degree to which the results of a test guide clinical management. For genetic testing, clinical utility includes establishing a diagnosis that obviates the need for additional workup or guiding surveillance or treatment. Test results may also be used as a basis for genetic counseling. For some disorders, genetic testing is possible but the test results do not add to the clinical assessment. If the diagnosis and genetic implications are already clear, it might not be necessary to pursue genetic testing.

PREDICTIVE TESTING

Predictive genetic testing involves performing a test in a person who is at risk for developing a genetic disorder (presymptomatic), usually on the basis of family history, yet who does not manifest signs or
symptoms. This is usually done for disorders that display age-dependent penetrance; the likelihood of manifesting signs and symptoms increases with age, as in cancer or Huntington disease.

A major caution with predictive testing is that the presence of a gene mutation does not necessarily mean that the disease will develop. Many of the disorders with age-dependent penetrance display incomplete penetrance. A person who inherits a mutation might never develop signs of the disorder. There is concern that a positive DNA test could result in stigmatization of the person and might not provide information that will guide medical management. Stigmatization might include psychological stress, but it could also include discrimination, including denial of health, life, or disability insurance, or employment (see Chapter 78).

It is generally agreed that predictive genetic tests should be performed for children if the results of the test will benefit the medical management of the child. Otherwise, the test should be deferred until the child has an understanding of the risks and benefits of testing and can provide informed consent. Individual states offer varying degrees of protection from discrimination on the basis of genetic testing. A major milestone in the prevention of genetic discrimination was the passage of the Genetic Information Nondiscrimination Act (GINA) in 2008, which is a federal law that prohibits discrimination in health coverage or employment based on genetic information; it does not protect against refusal of life insurance.

**PREDISPOSITIONAL TESTING**

It is expected that genetic tests will become available that will predict risk of disease. Common disorders are multifactorial in etiology; there may be many different genes that contribute to risk of any specific condition (see Chapter 82). Most of the genetic variants that have been found to correlate with risk of a common disease add small increments of relative risk, probably in most cases too little to guide management. It is possible that further discovery of genes that contribute to common disorders will reveal examples of variants that convey more significant levels of risk. It is also possible that testing several genes together will provide more information about risk than any individual gene variant would confer. The rationale for predispositional testing is that the results would lead to strategies aimed at risk reduction as part of a personalized approach to healthcare maintenance. This might include avoidance of environmental exposures that would increase risk of disease (cigarette smoking and α1-antitrypsin deficiency), medical surveillance (familial breast cancer and mammography), or, in some cases, pharmacologic (statins and hypercholesteremia) treatment. The value of predispositional testing will need to be critically appraised through outcomes studies as these tests are developed.

**PHARMACOGENETIC TESTING**

Polymorphisms in drug metabolism genes can result in distinctive patterns of drug absorption, metabolism, excretion, or effectiveness (see Chapters 59 and 82). Knowledge of individual genotypes will guide pharmacologic therapy, allowing customization of choice of drug and dosage to avoid toxicity and provide a therapeutic response. An example of this is testing for polymorphisms within the methylenetetrahydrofolate reductase (MTHFR) gene for susceptibility of potentially increased toxicity to methotrexate antimetabolite therapy for treatment of acute lymphoblastic leukemia.

### 77.1 Genetic Counseling

**Brendan Lee**

Genetic counseling is a communication process in which the genetic contribution to health is explained, along with specific risks of transmission of a trait and options to manage the condition and its inheritance (Table 77-3). The counselor is expected to present information in a neutral, nondirective manner and to provide support to the individual and family to cope with decisions that are made.

<table>
<thead>
<tr>
<th>Table 77-3</th>
<th>Indications for Genetic Counseling</th>
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<tr>
<td>Advanced parental age</td>
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<tr>
<td>Maternal age ≥35 yr</td>
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<td>Paternal age ≥250 yr</td>
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<td>Previous child with or family history of</td>
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<tr>
<td>Congenital abnormality</td>
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<tr>
<td>Dysmorphology</td>
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<td>Intellectual disability</td>
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<td>Isolated birth defect</td>
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<tr>
<td>Metabolic disorder</td>
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<td>Chromosome abnormality</td>
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<td>Single-gene disorder</td>
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<tr>
<td>Adult-onset genetic disease (presymptomatic testing)</td>
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<tr>
<td>Cancer</td>
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<td>Huntington disease</td>
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<tr>
<td>Consanguinity</td>
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<td>Teratogen exposure (occupational, abuse)</td>
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<tr>
<td>Repeated pregnancy loss or infertility</td>
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<tr>
<td>Pregnancy screening abnormality</td>
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<tr>
<td>Maternal serum Α-fetoprotein</td>
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<tr>
<td>Maternal triple or quad screen or variant of this test</td>
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<tr>
<td>Fetal ultrasonography</td>
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<td>Fetal karyotype</td>
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<td>Heterozygote screening based on ethnic risk</td>
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<tr>
<td>Sickle cell anemia</td>
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<tr>
<td>Tay-Sachs, Canavan, and Gaucher diseases</td>
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<tr>
<td>Thalassemias</td>
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<tr>
<td>Follow-up to abnormal neonatal genetic testing</td>
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<tr>
<td>Prior to whole genome or exome sequencing</td>
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<tr>
<td>Prior to preimplantation genetic testing</td>
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as much information and as many options as are available. The fourth situation is counselling prior to genome sequencing where the family is given options of what they want reported back to them (actionable, nonactionable incidental findings vs. a specific diagnosis).

GENETIC COUNSELING
Providing accurate information to families requires:
- Taking a careful family history and constructing a pedigree that lists the patient’s relatives (including abortions, stillbirths, deceased persons) with their sex, age, and state of health, up to and including 3rd-degree relatives.
- Gathering information from hospital records about the affected individual and, in some cases, about other family members.
- Documenting prenatal, pregnancy, and delivery histories.
- Reviewing the latest available medical, laboratory, and genetic information concerning the disorder.
- Performing a careful physical examination of the affected individual (photographs, measurements) and of apparently unaffected individuals in the family.
- Establishing or confirming the diagnosis by the diagnostic tests available.
- Giving the family information about support groups.
- Providing new information to the family as it becomes available (a mechanism for updating needs to be established).

Counseling sessions must include the specific condition, knowledge of the diagnosis of the particular condition, the natural history of the condition, the genetic aspects of the condition and the risk of recurrence, prenatal diagnosis and prevention, therapies and referral, support groups, and nondirective counseling.

Specific Condition or Conditions
If a specific diagnosis is made and confirmed, that should be discussed with the family and information should be provided in writing. However, often the disorder fits into a spectrum (e.g., one of many types of arthrogryposis) or the diagnosis is clinical rather than laboratory based. In those situations, the family needs to understand the limits of present knowledge and that additional research will probably lead to better information in the future.

Knowledge of the Diagnosis of the Particular Condition
Although it is not always possible to make an exact diagnosis, having a diagnosis as accurate as possible is important. Estimates of recurrence risk for various family members depend on an accurate diagnosis. When a specific diagnosis cannot be made (as in many cases of multiple congenital anomalies), the various possibilities in the differential diagnosis should be discussed with the family and empirical information should be provided. If specific diagnostic tests are available, they should be discussed. Often, empirical recurrence risks can be given even without a specific laboratory-based diagnosis. At the same time, even negative laboratory testing can further modify this risk.

Natural History of the Condition
It is very important to discuss the natural history of the specific genetic disorder in the family. Affected persons and their families have questions regarding the prognosis and potential therapy that can be answered only with knowledge of the natural history. If there are other possible diagnoses, their natural history may also be discussed. If the disorder is associated with a spectrum of clinical outcomes or complications, the worst and best scenarios, as well as treatment and referral to the appropriate specialist, should be addressed.

Genetic Aspects of the Condition and Recurrence Risk
The genetic aspects and risk of recurrence are important because all family members need to be aware of their reproductive choices. The genetics of the disorder can be explained with visual aids (e.g., diagrams of chromosomes). It is important to provide accurate occurrence and recurrence risks for various members of the family, including unaffected individuals. If a definite diagnosis cannot be made, it is necessary to use empirical recurrence risks. Counseling should give patients the necessary information to understand the various options and let the patients make their own informed decisions regarding pregnancy, adoption, artificial insemination, prenatal diagnosis, screening, carrier detection, and termination of pregnancy. It may be necessary to have more than 1 counseling session.

Prenatal Diagnosis and Prevention
Many different methods of prenatal diagnosis are available, depending on the specific genetic disorder (see Chapter 96). The use of ultrasonography allows prenatal diagnosis of anatomic abnormalities such as congenital heart defects. Amniocentesis and chorionic villus sampling are used to obtain fetal tissue for analysis of chromosomal abnormalities, biochemical disorders, and DNA studies. Maternal blood or serum sampling is used for some types of screening. Fetal cells can be retrieved from the umbilical cord or from maternal blood (free fetal DNA) for testing, although mothers might harbor cells from all previous pregnancies.

Therapies and Referral
A number of genetic disorders require the care of a specialist. Girls with Turner syndrome usually need to be evaluated by an endocrinologist. Prevention of known complications is a priority. The psychological adjustment of the family might require specific intervention. When to discuss the diagnosis of a chronic disease with the patient is always a difficult decision. The decision to do so should always involve the parents and an assessment of the maturity and capacity of the child or adolescent.

Alternative medicines or nontraditional therapies are often brought to attention by parents after exhaustive Internet searches. Such treatments should not necessarily be dismissed out of hand because the physician and counselor should serve as an important resource for helping parents navigate the maze of nonstandard treatments. Instead, the relative merits of treatments should be framed in the context of cost and benefit, scientific rationale, evidence from controlled and/or observational studies, the placebo effect, safety of the treatment, and the gaps in our own scientific knowledge base.

Support Groups
A large number of community lay support groups have been formed to provide information and to fund research on specific genetic and nongenetic conditions. An important part of genetic counseling is to give information about these groups to patients and to suggest a contact person for the families. Many groups have established websites with very helpful information; it is important to stress to families that their individual disease course will be unique.

Follow-up
Families should be encouraged to continue to ask questions and keep up with new information about the specific disorder. New developments often influence the diagnosis and therapy of specific genetic disorders. Lay support groups are a good source of new information.

Nondirective Counseling
Genetic counseling is usually nondirective; choices about reproduction are left to the family to decide what is right for them. The role of the counselor (physician, genetic counselor, nurse, medical geneticist) is to provide information in understandable terms and outline the range of options available.

77.2 Management and Treatment of Genetic Disorders

Brendan Lee

Genetic conditions are often chronic disorders; few are amenable to curative therapies. Nevertheless, many management options are
available. All patients and families should be provided information about the disorder, genetic counseling, anticipatory guidance, and appropriate medical surveillance. Surgical management is available for many conditions that are associated with congenital anomalies or predisposition to tumors.

Resources for patients include the National Organization of Rare Disorders (www.rarediseases.org), the Genetic Alliance (www.geneticalliance.org), the National Library of Medicine (www.nlm.nih.gov/medlineplus/geneticdisorders.html), and a large number of disease-specific websites. A current listing of federally and privately funded clinical trials, including many for genetic diseases, is available at www.ClinicalTrials.gov.

Specific medical therapies for genetic disorders can be classified into physiologic and replacement therapies. Much effort is currently focused in developing gene and cell therapies.

PHYSIOLOGIC THERAPIES

Physiologic therapies attempt to ameliorate the phenotype of a genetic disorder by modifying the physiology of the affected individual. The underlying defect itself is not altered by treatment. Physiologic therapies are used in the treatment of inborn errors of metabolism (see Chapter 84). These include dietary manipulation, such as avoiding phenylalanine by persons with phenylketonuria; coenzyme supplementation for some patients with methylmalonic acidemia and mitochondrial diseases; stimulation of alternative pathways to excrete ammonia for those with urea cycle disorders; bisphosphonate treatment for those with osteogenesis imperfecta to reduce bone fractures; and avoiding cigarette smoking by persons with α1-antitrypsin deficiency. Physiologic treatments can be highly effective, but they usually need to be maintained for a lifetime because they do not affect the underlying genetic disorder. Many of these treatments are most effective when begun early in life before irreversible damage has occurred. This is the rationale for comprehensive newborn screening for inborn errors of metabolism.

Many physiologic therapies use small-molecule pharmaceuticals (e.g., to remove ammonia in those with urea cycle disorders). Pharmacologic treatments directly target a defective cellular pathway that is altered by an abnormal or a missing gene product. However, there are relatively few such therapies. One example is the development of imatinib, a small molecule tyrosine kinase inhibitor developed specifically to target the biologic pathway altered in chronic myelogenous leukemia (CML). CML is usually associated with a chromosome 9,22 translocation (the Philadelphia chromosome) that creates a fusion of the BCR protein and the Abl oncogene. Imatinib is a small molecule that blocks the adenosine triphosphate binding in the fusion protein; it is highly effective in treatment of CML and several other malignancies. Other examples include large-molecule biologics such as “humanized” monoclonal antibodies.

REPLACEMENT THERAPIES

Replacement therapies include replacement of a missing metabolite, an enzyme, an organ, or even a specific gene.

Enzyme Replacement

Enzyme replacement therapy is a component of the treatment of cystic fibrosis to manage intestinal malabsorption. Pancreatic enzymes are easily administered orally, because they must be delivered to the gastrointestinal tract.

Enzyme replacement strategies are effective for some lysosomal storage disorders. Enzymes are targeted for the lysosome by modification with mannose-6-phosphate, which binds to a specific receptor. This receptor is also present on the cell surface, so lysosomal enzymes with exposed mannose-6-phosphate residues can be infused into the blood and are taken into cells and transported to lysosomes. Enzyme replacement therapies are available for Gaucher disease and Fabry disease, some mucopolysaccharidoses (I, II, VI), Niemann-Pick disease type C, and Pompe disease.

One complication of enzyme replacement therapy is antibody response to the enzyme. The magnitude of this response is not always predictable and varies depending on the enzyme preparation and the disease. In most cases, the patient’s antibody response does not affect the treatment’s efficacy (e.g., in Gaucher disease), but in other situations it may be a significant hurdle (e.g., in Pompe disease).

Transplantation

Cell and organ transplantation are potentially effective approaches to replacement of a defective gene. Aside from transplantation to replace damaged tissues, transplantation of stem cells, liver, or bone marrow is also used for several diseases, mainly inborn errors of metabolism, and hematologic or immunologic disorders. A successful transplant is essentially curative, though there may be significant risks and side effects (see Chapters 135-139). Cell and tissue transplantation are effective in many clinical scenarios, but there is always short-term morbidity, often associated with either surgical (liver) or preparative (bone marrow) regimens, and long-term morbidity related to chronic immunosuppression and graft failure. Bone marrow transplantation is the best example of stem cell therapy, but much effort is focused on identifying, characterizing, expanding, and using other tissue stem cells for regenerative therapies.

Alternatively, research has focused on replacing a defective gene (gene therapy). In theory, if we can target the specific tissue that has a deficiency in the gene or gene product, this can offer a less invasive means of achieving a cure of a genetic disorder. Ultimately, gene therapy depends on the unique interaction of the disease pathophysiology, which is specific to the patient, and the gene delivery vehicle.

Gene-transfer vehicles include viral and nonviral approaches. Most human clinical trials have used viral vectors because of their efficiency of tissue transduction. In some diseases, such as X-linked and adenosine deaminase-deficient severe combined immunodeficiency, clinical gene therapy is a viable and effective option (see Chapter 126.1). Preliminary results suggest that gene therapy (intraocular delivery) may be effective for Leber congenital amaurosis.

Bibliography is available at Expert Consult.
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Since the completion of the Human Genome Project, we have seen an unprecedented expansion in our understanding of how human health is impacted by variations in genomic sequence and epigenetic, non-sequence-based, changes that affect gene expression. This period has also seen the development and implementation of new clinical tests that have made it easier for physicians to detect such changes. In addition, this period has seen a dramatic increase in the availability of information about the genetic aspects of pediatric diseases, particularly on the Internet (Table 78-1).

THE BURDEN OF GENETIC DISORDERS IN CHILDHOOD

Medical problems associated with genetic disorders can appear at any age with the most obvious and serious problems typically manifesting in childhood. It has been estimated that 53/1,000 children and young adults can be expected to have diseases with an important genetic component. If congenital anomalies are included, the rate increases to 79/1,000. In 1978, it was estimated that just over half of admissions to
pediatric hospitals were for a genetically determined condition. By 1996, owing to changes in healthcare delivery and a greater understanding of the genetic basis of many disorders, that percentage rose to 71% in 1 large pediatric hospital in the United States, and 96% of chronic disorders leading to admission had an obvious genetic component or were influenced by genetic susceptibility. Major categories of genetic disorders include single-gene, genomic, chromosomal, and multifactorial conditions.

Individually, single-gene disorders are rare, but collectively they represent an important contribution to childhood disease. The hallmark of a single-gene disorder is that the phenotype is overwhelmingly determined by changes that affect an individual gene. The phenotypes associated with single-gene disorders can vary from one patient to another based on the severity of the change affecting the gene and additional modifications caused by genetic, environmental, and/or stochastic factors. This feature of genetic disease is termed variable expressivity. Common single-gene disorders include sickle cell anemia and cystic fibrosis.

Single-gene disorders tend to occur when changes in a gene have a profound effect on the quantity of the gene product produced—even too much or too little—or the function of the gene product—either a loss of function or a harmful gain of function. Single-gene disorders can be caused by de novo changes that are not found in the unaffected parents of the affected individual or they may be caused by inherited changes. When a single-gene disorder is known to be caused by changes in only 1 gene or a small number of individual genes, searching for deleterious changes is most often performed by directly sequencing that gene and, in some cases, looking for small deletions and/or duplications. When multiple genes can potentially cause a particular disorder, it is sometimes more efficient and cost effective to screen large numbers of disease causing genes using a disease-specific panel that takes advantage of next generation sequencing technology than to screen genes individually. When such panels are not available, or when the diagnosis is in question, physicians may consider screening the protein coding regions of all genes by whole exome sequencing on a clinical basis. Indeed in many circumstances, whole exome sequencing is less expensive than sequencing multiple individual genes. In the future, whole genome sequencing—in which an individual’s entire genome is sequenced—may become a valid clinical option as the cost of such tests fall and our ability to interpret the clinical consequences of thousands of changes that are identified in such tests improves.

The risk of having a child with a particular single gene disorder can vary from one population to another. In some cases this is the result of a founder effect, in which a specific change affecting a disease-causing gene becomes relatively common in a population derived from a small number of founders. This high frequency is maintained when there is relatively little interbreeding with persons outside of that population because of social, religious, or physical barriers. This is the case for Tay-Sachs disease in Ashkenazi Jews and French Canadians. Other changes may be subject to positive selection when found in the heterozygous carrier state. In this case, carriers of a genetic change (heterozygotes) have a survival advantage over noncarriers. This can occur even when individuals who inherit 2 copies of the change (homozygotes) have severe medical problems. This type of positive selection is evident among individuals in sub-Saharan Africa who carry a hemoglobin mutation that confers relative resistance to malaria but causes sickle cell anemia in homozygotes.

Genomic disorders are a group of diseases caused by alterations in the genome, including deletions (copy number loss), duplications (copy number gain), inversions (altered orientation of a genomic region) and chromosomal rearrangements (altered location of a genomic region). Contiguous gene disorders are caused by changes that affect two or more genes that contribute to the clinical phenotype and are located near each other on a chromosome. DiGeorge syndrome, which is caused by deletions of genes located on chromosome 22q11, is a common example. Some genomic disorders are associated with distinctive phenotypes whose pattern can be recognized clinically. Other genomic disorders do not have a distinctive pattern of anomalies, but can cause developmental delay, cognitive impairment, structural birth defects, abnormal growth patterns and changes in physical appearance. Fluorescent in situ hybridization (FISH) can provide information about the copy number and location of a specific genomic region. Array-based copy number detection assays can be used to screen for chromosomal deletions (large and small) and duplication across the genome but do not provide information about the orientation or location of genomic regions. A chromosome analyses (karyotyping) can detect relatively large chromosomal deletions and duplications and can also be useful in identifying inversions and chromosomal rearrangements even when they are copy-number neutral.
changes that do not result in a deletion or duplication of genomic material. Deletions, duplications, and chromosomal rearrangements that affect whole chromosomes, or large portions of a chromosome, are commonly referred to as chromosomal disorders. One of the most common chromosomal disorders is Down syndrome, which is most commonly associated with the presence of an extra copy, or trisomy, of an entire chromosome 21. When all or a part of a chromosome is missing, the disorder is referred to as monosomy. Translocations are a type of chromosomal rearrangement in which a genomic region from 1 chromosome is transferred to a different location on the same chromosome or on a nonhomologous chromosome. Translocations can be balanced, meaning that no genetic material has been lost or gained, or they can be unbalanced, in which case some genetic material has been deleted or duplicated. Chromosomal disorders can often be identified on a chromosome analysis (karyotype) or by FISH. Evidence of a chromosomal disorder may also be revealed by an array-based copy number detection assays if genetic material has been gained or lost.

In some cases, only a portion of cells that make up a person's body are affected by the single gene defect, the genomic disorder or the chromosomal defect. This is referred to as mosaicism and indicates that the individual's body is made up of 2 or more distinct cell populations. Polygenic disorders are caused by the cumulative effects of changes or variations in more than 1 gene. Multifactorial disorders are caused by the cumulative effects of changes or variations in multiple genes and/or the combined effects of both genetic and environmental factors. Spina bifida and isolated cleft lip or palate are common birth defects that display multifactorial inheritance patterns. Multifactorial inheritance is seen in many common pediatric disorders, such as asthma and diabetes mellitus. These traits can cluster in families but do not have a mendelian pattern of inheritance (see Chapter 80). In most cases, the genetic changes or variations that are contributing to a particular case are unknown and genetic counseling is based on empirical data.

**THE CHANGING PARADIGM OF GENETICS IN MEDICINE**

Genetic testing is increasingly available for a wide variety of both rare and relatively common genetic disorders. Genetic testing is commonly used in pediatric medicine to resolve uncertainty regarding the underlying etiology of a child's medical problems and provides a basis for improved genetic counseling and possibly specific therapy. Even in cases where a specific treatment is not available, identifying a genetic cause can aid physicians in providing individuals and family with accurate prognostic and recurrence risk information and usually helps to relieve unfounded feelings of guilt and/or stem the tide of misdirected blame.

Genetic tests will ultimately come to underlie a high proportion of medical decisions and will be seamlessly incorporated into routine medical care. Although most genetic testing is presently aimed at identifying or confirming a diagnosis, in the future, genetic testing may find wider application as a means of determining if an individual is predisposed to develop a particular disease. Another area in which genetic testing could make a significant impact is on individualized drug treatment. It has long been known that genetic variation in the enzymes involved in drug metabolism underlies differences in the therapeutic effect and toxicity of some drugs. As the genetic changes that underlie these variations are identified, new genetic tests may be developed that will allow physicians to tailor treatments based on individual variations in drug metabolism, responsiveness, and susceptibility to toxicity (see Chapter 59). It is likely that the expansion of such testing will depend, at least in part, on the extent to which such testing can be linked to strategies to prevent disease or improve outcome (see Chapter 77). If such links can be made, it could usher in a new era of personalized medical treatment.

Long-standing and highly successful carrier screening programs have existed for disorders such as Tay-Sachs disease and many other rare single-gene disorders that are prevalent in specific populations. Couples are commonly offered screening for a variety of conditions, in part based on ancestry (Tay-Sachs disease, hemoglobinopathies, cystic fibrosis). Couples found to be at increased risk for such disorders can be offered preconception or prenatal testing aimed at detecting specific disease causing mutations.

Prenatal screening is routinely offered for chromosomal disorders such as trisomy 13, trisomy 18, and Down syndrome. An increasing number of pregnancies affected by these and other genetic disorders are being recognized by noninvasive screening tests of maternal serum in the first and second trimesters and by fetal ultrasound. When genetic disorders are suspected, chorionic villus sampling at 10-12 wk of gestation or by amniocentesis at 16-18 wk of gestation can provide material for genetic testing. Approaches to noninvasive prenatal diagnosis by sampling of cell-free fetal DNA or fetal cells in maternal blood are also becoming available. When a couple is at risk for a specific genetic defect, preimplantation genetic diagnosis can sometimes be used to select unaffected early embryos, which are then implanted as part of an in vitro fertilization procedure.

Although prenatally obtained genetic material can be used to identify single-gene disorders, genomic disorders, and chromosomal anomalies, the information obtained on any pregnancy depends on the tests that are ordered. It is important that physicians select the most appropriate prenatal tests and that couples understand both the limitations of these tests and that no amount of genetic testing can guarantee the birth of a healthy child.

Specific treatments are not available for the majority of genetic disorders. However, there are some important exceptions. Inborn errors of metabolism were the first genetic disorders to be recognized, and many are amenable to treatment by dietary manipulation (see Chapter 84). These conditions result from genetically determined deficiency of specific enzymes, leading to the buildup of toxic substrates and/or deficiency of critical end products.

Individual metabolic disorders tend to be very rare, but their combined impact on the pediatric population is significant. Tandem mass spectrometry has made it relatively inexpensive to screen for a large number of these disorders in the newborn period. Use of this technology not only dramatically increases the number of metabolic disorders identified within a population but also allows treatment to be initiated at a much earlier stage in development (see Chapters 77 and 84).

Another area where progress has been made regarding genetic therapies has been in the treatment of lysosomal storage disorders. These are a group of metabolic diseases caused by defects in lysosomal function. Lysosomes are cellular organelles that contain specific digestive enzymes. Some of these disorders that were lethal or associated with intractable chronic illness can now be treated using specially modified enzymes that are administered by intravenous infusion. These enzymes are then taken up by cells and incorporated into lysosomes. Conditions such as Gaucher disease and Fabry disease are routinely treated using enzyme replacement, and similar therapies are being developed for other lysosomal disorders.

Therapeutic advances are also being made in the treatment of nonmetabolic genetic disorders. Improvements in surgical techniques and intensive care medicine are extending the survival of children with life-threatening birth defects like congenital diaphragmatic hernia and severe cardiac defects. In many cases, the life expectancy of children with debilitating genetic disorders is also increasing. A good example is the increasing life expectancy of individuals with cystic fibrosis, largely owing to improvements in antibiotic therapy as well as the management of chronic pulmonary disease and malabsorption. A major consequence of these advances is that an increasing percentage of affected patients is surviving into adulthood, creating a need to transition care from pediatric to adult providers.

Gene-replacement therapies have long been anticipated. However, it has proved difficult to develop safe and effective approaches for inserting genes into diseased tissues in a way that allows physiologically meaningful levels of gene expression to be maintained over long periods. Stem cell-based therapies have also been touted as a potential treatment for a number of intractable disorders, but clear evidence that such therapies are effective has yet to materialize.
ETHICS ISSUES

Like all medical care, genetic testing, diagnosis, and treatment should be performed confidentially. Nothing is as personal as one's genetic information, and all efforts should be made to avoid any stigma for the patient. Many people fear that results of genetic testing will put them, or their child, at risk for genetic discrimination. Genetic discrimination occurs when people are treated unfairly because of a difference in their DNA that suggests that they have a genetic disorder or are at an increased risk of developing a certain disease. In the United States, the Genetic Information Nondiscrimination Act of 2008 protects individuals from genetic discrimination at the hands of health insurers and employers, but does not extend protection against discrimination from providers of life, disability, or long-term care insurance.

Like all medical decision-making, the decisions about genetic testing should be based on a careful evaluation of the potential benefits and risks. In the pediatric setting, these decisions may be more difficult because physicians and parents are often called on to make decisions for a child who cannot directly participate in discussions about the testing. Molecular diagnostic tests are often used to diagnose malformation syndromes, cognitive delay, or other disabilities wherein there is a clear benefit to the child. In other cases, such as genetic testing for susceptibility to adult-onset diseases, it is appropriate to wait until the child or adolescent is mature enough to weigh the pros and cons and make his or her own decisions about genetic testing.

Policies regarding genetic testing of children have been developed collaboratively by the American Academy of Pediatrics (AAP) and the American College of Medical Genetics and Genomics (ACMG; Pediatrics 131[3]:620-622, 2013). These recommendations are outlined here:

1. Decisions about whether to offer genetic testing and screening should be driven by the best interest of the child.

2. Genetic testing is best offered in the context of genetic counseling. Genetic counseling can be performed by clinical geneticists, genetic counselors, or any other health care provider with appropriate training and expertise. The AAP and ACMG support the expansion of educational opportunities in human genomics and genetics for medical students, residents, and practicing pediatric primary care providers.

Diagnostic Testing

3. In a child with symptoms of a genetic condition, the rationale for genetic testing is similar to that of other medical diagnostic evaluations. Parents or guardians should be informed about the risks and benefits of testing, and their permission should be obtained. Ideally, and when appropriate, the assent of the child should be obtained.

4. When performed for therapeutic purposes, pharmacogenetic testing of children is acceptable, with permission of parents or guardians and, when appropriate, the child's assent. If a pharmacogenetic test result carries implications beyond drug targeting or dose-responsiveness, the broader implications should be discussed before testing.

Newborn Screening

5. The AAP and ACMG support the mandatory offering of newborn screening for all children. After education and counseling about the substantial benefits of newborn screening, its remote risks, and the next steps in the event of a positive screening result, parents should have the option of refusing the procedure, and an informed refusal should be respected.

Carrier Testing

6. The AAP and ACMG do not support routine carrier testing in minors when such testing does not provide health benefits in childhood. The AAP and ACMG advise against school-based testing or screening programs, because the school environment is unlikely to be conducive to voluntary participation, thoughtful consent, privacy, confidentiality, or appropriate counseling about test results.

7. For pregnant adolescents or for adolescents considering reproduction, genetic testing and screening should be offered as clinically indicated, and the risks and benefits should be explained clearly.

Predictive Genetic Testing

8. Parents or guardians may authorize predictive genetic testing for asymptomatic children at risk of childhood-onset conditions. Ideally, the assent of the child should be obtained.

9. Predictive genetic testing for adult-onset conditions generally should be deferred unless an intervention initiated in childhood may reduce morbidity or mortality. An exception might be made for families for whom diagnostic uncertainty poses a significant psychosocial burden, particularly when an adolescent and his or her parents concur in their interest in predictive testing.

10. For ethical and legal reasons, healthcare providers should be cautious about providing predictive genetic testing to minors without the involvement of their parents or guardians, even if a minor is mature. Results of such tests may have significant medical, psychological, and social implications, not only for the minor but also for other family members.

Histocompatibility Testing

11. Tissue compatibility testing of minors of all ages is permissible to benefit immediate family members but should be conducted only after thorough exploration of the psychosocial, emotional, and physical implications of the minor serving as a potential stem cell donor. A donor advocate or similar mechanism should be in place from the outset to avert coercion and safeguard the interests of the child.

Adoption

12. The rationale for genetic testing of children in biological families should apply for adopted children and children awaiting placement for adoption. If a child has a known genetic risk, prospective adoptive parents must be made aware of this possibility. In rare cases, it may be in a child's best interest to undergo predictive genetic testing for a known risk before adoption to ensure the child's placement with a family capable of and willing to accept the child's potential medical and developmental challenges. In the absence of such indications, genetic testing should not be performed as a condition of adoption.

Disclosure

13. At the time of genetic testing, parents or guardians should be encouraged to inform their child of the test results at an appropriate age. Parents or guardians should be advised that, under most circumstances, a request by a mature adolescent for test results should be honored.

14. Results from genetic testing of a child may have implications for the parents and other family members. Healthcare providers have an obligation to inform parents and the child, when appropriate, about these potential implications. Healthcare providers should encourage patients and families to share this information and offer to help explain the results to the extended family or refer them for genetic counseling.

15. Misattributed paternity, use of donor gametes, adoption, or other questions about family relationships may be uncovered "incidentally" whenever genetic testing is performed, particularly when testing multiple family members. This risk should be discussed, and a plan about disclosure or nondisclosure should be in place before testing.

Direct-to-Consumer Testing

16. The AAP and ACMG strongly discourage the use of direct-to-consumer and home-kit genetic testing of children because of the lack of oversight on test content, accuracy, and interpretation.

Bibliography is available at Expert Consult.
Bibliography
The Human Genome Project, culminated in the sequencing of the human genome and greatly expanded our ability to study human genes and to explore the roles of genes in both rare and common disorders. Over time, it has also become apparent that the genome includes far more than a coded store of information to produce proteins.

The human genome has approximately 25,000 genes that encode the wide variety of proteins found in the human body. Reproductive or germ line cells contain 1 copy (N) of this genetic complement and are haploid, whereas somatic (non-germ line) cells contain 2 complete copies (2N) and are diploid. Genes are organized into long segments of DNA, which, during cell division, are compacted into intricate structures together with proteins to form chromosomes. Each somatic cell has 46 chromosomes: 22 pairs of autosomes, or nonsex chromosomes, and 1 pair of sex chromosomes (XY in a male, XX in a female). Germ cells (ova or sperm) contain 22 autosomes and 1 sex chromosome, for a total of 23. At fertilization, the full diploid chromosome complement of 46 is again realized in the embryo.

Most of the genetic material is contained in the cell’s nucleus. The mitochondria (the cell’s energy-producing organelles) contain their own unique genome. The mitochondrial chromosome consists of a double-stranded circular piece of DNA, which contains 16,568 base pairs (bp) of DNA and is present in multiple copies per cell. The proteins that occupy the mitochondria are produced either in the mitochondria, using information contained in the mitochondrial genome, or are produced outside of the mitochondria, using information contained in the nuclear genome and transported into the organelle. Sperm do not usually contribute mitochondria to the developing embryo, so all mitochondria are maternally derived and a child’s mitochondrial genetic makeup derives exclusively from the child’s biological mother.

**FUNDAMENTALS OF MOLECULAR GENETICS**

The central tenet of molecular genetics is that information encoded in DNA, predominantly located in the cell nucleus, is transcribed into messenger RNA (mRNA), which is then transported to the cytoplasm, where it is translated into protein. A gene is a unit that includes a regulatory region and a coding region that stores information corresponding to the sequence of amino acids in a specific protein.

DNA consists of a pair of chains of a sugar-phosphate backbone linked by pyrimidine and purine bases to form a double helix (Fig. 79-1). The sugar in DNA is deoxyribose. The pyrimidines are cytosine (C) and thymine (T); the purines are guanine (G) and adenine (A). The bases are linked by hydrogen bonds such that A always pairs with T and G with C. Each strand of the double helix has polarity, with a free phosphate at one end (5′) and an unbounded hydroxyl on the sugar at the other end (3′). The 2 strands are oriented in opposite polarity in the double helix.

The replication of DNA follows the pairing of bases in the parent DNA strand. The original 2 strands unwind by breaking the hydrogen bonds between base pairs. Free nucleotides, consisting of a base attached to a sugar-phosphate, form new hydrogen bonds with their complementary bases on the parent strand; new phosphodiester bonds are created by the enzyme DNA polymerase. Replication of chromosomes begins simultaneously at multiple sites, forming replication bubbles that expand bidirectionally until the entire DNA molecule (chromosome) is replicated. Errors in DNA replication, or mutations induced by environmental mutagens such as irradiation or chemicals, are detected and potentially corrected by DNA repair systems.

A prototypical gene consists of a regulatory region, segments called exons that encode the amino acid sequence of a protein, and intervening segments called introns (Fig. 79-2). Transcription starts at the promoter region and continues through the entire length of the gene to form mRNA. The introns are removed and the exons spliced together to form a mature message, which is exported to the cytoplasm. There the mRNA is bound to ribosomes and translated into protein.

Transcription is initiated by attachment of RNA polymerase to the promoter site upstream of the beginning of the coding sequence. Specific proteins bind to the region to either repress or activate transcription by opening up the chromatin, which is a complex of DNA and histone proteins. It is the action of these regulatory proteins (transcription factors) that determines, in large part, when a gene is turned on or off. Some genes are also turned on and off by methylation of cytosine bases that are adjacent to guanines (CpG [cytosine-phosphate-guanine] bases). Methylation is an example of an epigenetic change, meaning a change that can affect gene expression, and possibly the characteristics of a cell or organism, but that does not involve a change in the underlying genetic sequence. Gene regulation is flexible and responsive, with genes being turned on or off during development and in response to internal and external environmental conditions and stimuli.

Transcription proceeds through the full length of the gene, synthesizing mRNA in a 5′ to 3′ direction. RNA, like DNA, is a sugar-phosphate chain with pyrimidines and purines. In RNA, the sugar is ribose and uracil replaces the thymine found in DNA. The RNA reads off 1 strand of DNA to copy a complementary RNA sequence. A “cap” consisting of 7-methylguanosine is added to the 5′ end of the RNA in a 5′-5′ bond and, for most transcripts, several hundred adenine bases are enzymatically added to the 3′ end after transcription.

mRNA processing occurs in the nucleus and consists of excision of the introns and splicing together of the exons. Specific sequences at the start and end of introns mark the sites where the splicing machinery will act on the transcript. In some cases, there may be tissue-specific
Figure 79-2 Flow of information from DNA to RNA to protein for a hypothetical gene with three exons and two introns. Within the exons, blue indicates the coding sequences. Steps include transcription, RNA processing and splicing, RNA transport from the nucleus to the cytoplasm, and translation. (From Nussbaum RL, McInnis RR, Willard HF, Hamosh A, editors: Thompson & Thompson genetics in medicine, ed 7, Philadelphia, 2007, Saunders/Elsevier, Fig 3.5, p. 31.)

patterns to splicing, so that the same primary transcript can produce multiple distinct proteins.

The processed transcript is next exported to the cytoplasm, where it binds to ribosomes, which are complexes of protein and RNA. The genetic code is then read in triplets of bases, each triplet corresponding with a specific amino acid or providing a signal that terminates translation. The triplet codons are recognized by transfer RNAs that include complementary anticodons and bind the corresponding amino acid, delivering it to the growing peptide. A new amino acid is enzymatically attached to the peptide; each time an amino acid is added, the ribosome moves one triplet codon step along the mRNA. Eventually a stop codon is reached, at which point translation ends and the peptide is released. In some proteins, there are posttranslational modifications, such as attachment of sugars (glycosylation); the protein is then delivered to its destination within or outside the cell by trafficking mechanisms that recognize portions of the peptide.

An emerging layer of complexity and genetic regulation is that of noncoding RNAs. This refers to RNAs that are transcribed from DNA but are not translated into proteins. Noncoding RNAs function in mediating splicing and the processing of coding RNAs in the nucleus and the translation of coding RNAs in ribosomes. The roles of large noncoding RNAs (>200 bp) and short noncoding RNAs (<200 bp) extend beyond these processes to impact a diverse set of biologic functions including regulation of gene expression. For example, microRNAs (miRNAs) are a class of small RNAs that control gene expression in the cell by directly targeting specific sets of coding RNAs by direct RNA–RNA binding. This RNA–RNA interaction can lead to degradation of the target coding RNA or inhibition of translation of the protein specified by that coding RNA. miRNAs, in general, target and regulate several hundred mRNAs.

GENETIC VARIATION

The process of producing protein from a gene is subject to disruption at multiple levels owing to alterations in the coding sequence (Fig. 79-3). Changes in the regulatory region can lead to altered gene expression, including increased or decreased rates of transcription, failure of gene activation, or activation of the gene at inappropriate times or in inappropriate cells. Changes in the coding sequence can lead to substitution of one amino acid for another (missense mutation or nonsynonymous) or creation of a stop codon in the place of an amino acid codon. Overall, missense or nonsense mutations are the most common (~56% of mutations); small deletions or insertions represent approximately 24% of mutations (Table 79-1). Some single-base changes do not affect the amino acid (silent or wobble mutation or synonymous), because there may be several triplet codons that correspond with a single amino acid. Amino acid substitutions can have a profound effect on protein function if the chemical properties of the substituted amino acid are markedly different from the usual one. Other substitutions can have a subtle or no effect on protein function, particularly if the substituted amino acid is chemically similar to the original one.

Genetic changes can also include insertions or deletions. Insertions or deletions of a nonintegral multiple of 3 bases into the coding sequence leads to a frameshift, altering the grouping of bases into triplets. This leads to translation of an incorrect amino acid sequence and often a premature stop to translation. Insertion or deletion of an
Gene, and a 50% decrease in gene function results in an abnormal phenotype. Hence, haploinsufficient phenotypes are, by definition, dominantly inherited. Loss-of-function mutations can also have a dominant negative effect when the abnormal protein product actively interferes with the function of the normal protein product. Both of these situations lead to diseases inherited in a dominant fashion (see Chapter 80). In other cases, loss-of-function mutation must be present in both copies of a gene before an abnormal phenotype results. This situation typically results in diseases inherited in a recessive fashion (see Chapter 80).

Gain-of-function mutations typically cause dominantly inherited diseases. These mutations can result in production of a protein molecule with an increased ability to perform a normal function or they

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*Some have been shown to cause aberrant splicing.

can confer a novel property on the protein. The gain-of-function mutation in achondroplasia, the most common of the disproportionate, short-limbed short stature disorders, exemplifies the enhanced function of a normal protein. Achondroplasia results from a mutation in the fibroblast growth factor receptor 3 gene (FGFR3), which leads to activation of the receptor, even in the absence of fibroblast growth factor. In sickle cell disease, an amino acid is substituted into the hemoglobin molecule that has little effect on the ability of the protein to transport oxygen. However, sickle hemoglobin chains have a novel property. Unlike normal hemoglobin, sickle hemoglobin chains aggregate under conditions of deoxygenation, forming fibers that deform the red cells.

In some cases the recognition of a specific constellation of features leads the clinician to suspect a specific microdeletion or microduplication syndrome. Examples of such disorders include Smith-Magenis, DiGeorge, and Williams syndromes. In other cases, the clinician may be alerted to this possibility by an unusually diverse array of clinical features in one patient or the presence of unusual features in a person with a known condition. Owing to the close physical proximity of a series of genes, different deletions involving the short arm of the X chromosome can produce individuals with various combinations of ichthyosis, Kallmann syndrome, ocular albinism, intellectual disability, chondrodysplasia punctata, and short stature.

DNA rearrangements can also take place in somatic cells-meaning that cells do not go on to produce ova or sperm. Rearrangements that occur in lymphoid cells are required for the formation of functional immunoglobulin in B cells and antigen-recognizing receptors on T cells. Large segments of DNA, which code for the variable and the constant regions of either immunoglobulin or the T-cell receptor, are physically joined at a specific stage in the development of an immunocompetent lymphocyte. These rearrangements take place during development of the lymphoid cell lineage in humans and result in the extensive diversity of immunoglobulin and T-cell receptor molecules. It is as a result of this postgermline DNA rearrangement that no 2 individuals, even if identical twins, are really identical, because mature lymphocytes from each will have undergone random DNA rearrangements at these loci.

Studies of the human genome sequence reveal that any 2 individuals differ in about 1 base in 1,000. Some of these differences are silent; some result in changes that explain phenotypic differences (hair or eye color, physical appearance); some have medical significance, causing single-gene disorders such as sickle cell anemia or explaining susceptibility to common pediatric disorders such as asthma. Genetic variants in a single gene that occur at a frequency of >1% in a population are often referred to as polymorphisms. These variations may be silent or subtle or have significant phenotypic effects.
GENOTYPE-PHENOTYPE CORRELATIONS IN GENETIC DISEASE

The term genotype is used to signify the internally coded, heritable information of an individual and can also be used to refer to which particular alternative version (allele) of a gene is present at a specific location (locus) on a chromosome. A phenotype is the observed structural, biochemical, and physiologic characteristics of an individual, determined by the genotype, and can also refer to the observed structural and functional effects of a mutant allele at a specific locus. Many mutations result in predictable phenotypes. In these cases, physicians can predict clinical outcomes and plan appropriate treatment strategies based on a patient's genotype.

The long QT syndrome exemplifies a disorder with predictable associations between a patient's genotype and his or her phenotype (see Chapter 435.5). Long QT syndrome is genetically heterogeneous, meaning that mutations in several different genes can cause the same disorder. The risk for cardiac events (syncope, aborted cardiac arrest, or sudden death) is higher with long QT syndrome mutations involving the KCNQ1 gene (63%) or the KCNH2 gene (46%) than among subjects with mutations in the SCN5A gene (18%). In addition, those with mutations involving KCNQ1 experience most of their episodes during exercise and rarely during rest or sleep. In contrast, individuals with mutations in KCNH2 and SCN5A are more likely to have episodes during sleep or rest, and rarely during exercise. Therefore, mutations in specific genes (genotype) are correlated with specific manifestations (phenotype) of long QT syndrome. These types of relationships are commonly referred to as genotype–phenotype correlations.

Mutations in the fibrillin-1 gene associated with Marfan syndrome represent another example of predictable genotype–phenotype correlations (see Chapter 702). Marfan syndrome is characterized by the combination of skeletal, ocular, and aortic manifestations, with the most devastating outcome being aortic root dissection and sudden death. Sixty-five exons make up the fibrillin-1 gene, and mutations have been found in almost all of these exons. The location of the mutation within the gene (genotype) might play a significant role in determining the severity of the condition (phenotype). Neonatal Marfan syndrome is caused by mutations in exons 24–27 and in exons 31 and 32, whereas milder forms are caused by mutations in exons 59–65 and in exons 37 and 41.

Genotype–phenotype correlations have also been observed in some complications of cystic fibrosis (CF; see Chapter 403). Although pulmonary disease is the major cause of morbidity and mortality, CF is a multisystem disorder that affects not only the epithelia of the respiratory tract but also the exocrine pancreas, intestine, male genital tract, hepatobiliary system, and exocrine sweat glands. CF is caused by mutations in the CF transmembrane conductance regulator (CFTR) gene. More than 1,600 different mutations have been identified. The most common is a deletion of 3 nucleotides that removes the amino acid phenylalanine (F) at the 508th position on the protein (AF508 mutation), which accounts for approximately 70% of all CF mutations and is associated with severe disease. The best genotype–phenotype correlations in CF are seen in the context of pancreatic function, with most common mutations being classified as either pancreatic sufficient or pancreatic insufficient. Persons with pancreatic sufficiency usually have either 1 or 2 pancreatic-sufficient alleles, indicating that pancreatic-sufficient alleles are dominant. In contrast, the genotype–phenotype correlation in pulmonary disease is much weaker, and persons with identical genotypes have wide variations in the severity of their pulmonary disease. This finding may be accounted for in part by genetic modifiers or environmental factors.

There are many disorders in which the effects of mutations on phenotype can be modified by changes in the other allele of the same gene, by changes in specific modifier genes, and/or variations in a number of unspecified genes (genetic background). When sickle cell anemia is coinherited with the gene for hereditary persistence of fetal hemoglobin, the sickle cell phenotypic expression is less severe. Modifier genes in CF can influence the development of congenital meconium ileus, or colonization with Pseudomonas aeruginosa. Modifier genes can also affect the manifestations of Hirschsprung disease, neurofibromatosis type 2, craniosynostosis, and congenital adrenal hyperplasia. The combination of genetic mutations producing glucose-6-phosphate dehydrogenase deficiency and longer versions of the TATAA element in the uridine diphosphate–glucoronoysltransferase gene promoter exacerbates neonatal physiologic hyperbilirubinemia.

HUMAN GENOME PROJECT

A rudimentary genetic map can be made using genetic linkage, which is based on the principle that alleles at 2 genetic loci that are located near each other segregate together in a family unless they are separated by genetic recombination. The frequency of recombination between the loci can be used to estimate the physical distance between points. Some of the first maps of the human genome were linkage maps based on a set of polymorphic genetic loci located along the entire human genome. Linkage analysis is still used to map the location of genetic changes responsible for phenotypic traits and genetic disorders that are inherited in a mendelian fashion.

In contrast to linkage maps, which are based on recombination frequencies, physical maps rely on overlapping DNA fragments to determine the location of loci with respect to one another. Several strategies can be used to create physical maps of a chromosomal region. In one strategy, segments of the region of interest with lengths from hundreds or thousands to a few million base pairs are isolated and placed in microorganisms such as bacteria or yeast. Common regions contained in different organism can then be identified and this information can be used to piece together a map composed of overlapping DNA pieces, each contained in a different microorganism. The pieces contained in each organism can then be sequenced to obtain the DNA sequence of the entire region. An alternative strategy involves breaking the entire genome into random fragments, sequencing the fragments, and then using a computer to order the fragments based on overlapping segments. This whole genome approach in combination with new next-generation sequencing technologies has resulted in a dramatic reduction in the cost of sequencing an individual's entire genome.

Analysis of the human genome has produced some surprising results. The number of genes is still not known precisely but appears to be around 25,000. This is fewer than had been expected and in the same range as many simpler organisms. The number of protein products encoded by the genome is greater than the number of genes. This is a result of the presence of alternative promoter regions, alternative splicing, and posttranslational modifications, which can allow a single gene to encode a number of protein products.

It is also apparent that most of the human genome does not encode protein, with <5% being transcribed and translated, though a much larger percentage may be transcribed without translation. Many transcribed sequences have not been translated but represent genes that encode RNAs that serve a regulatory role. A large fraction of the genome consists of repeated sequences that are interspersed among the genes. Some of these are transposable genetic elements that can move from place to place in the genome. Others are static elements that were expanded and dispersed in the past during human evolution. Other repeated sequences might play a structural role. There are also regions of genomic duplications. Such duplications are substrate for evolution, allowing genetic motifs to be copied and modified to serve new roles in the cell. Duplications can also play a role in chromosomal rearrangement, permitting nonhomologous chromosome segments to pair during meiosis and exchange material. This is another source of evolutionary change and a potential source of chromosomal instability leading to congenital anomalies or cancer. Low copy repeats also play an important role in causing genomic disorders. When low copy repeats flank unique genomic segments, these regions can be duplicated or deleted through a process known as nonallelic homologous recombination.

Availability of the entire human genomic sequence permits the study of large groups of genes, looking for patterns of gene expression or genome alteration. Microarrays permit the expression of thousands of genes to be analyzed on a small glass chip. Increasingly, studies of gene expression are being performed using next generation sequencing.
techniques to obtain information about all of the RNA transcripts in a tissue sample. In some cases the patterns of gene expression provide signatures for particular disease states, such as cancer, or change in response to therapy (Fig. 79-5).

Bibliography is available at Expert Consult.
Bibliography
Chapter 80  Patterns of Genetic Transmission
Daryl A. Scott and Brendan Lee

FAMILY HISTORY AND PEDIGREE NOTATION
The family history remains the most important screening tool for pediatricians in identifying a patient’s risk for developing a wide range of diseases, from multifactorial conditions, such as diabetes and attention-deficit disorder, to single-gene disorders such as sickle cell anemia and cystic fibrosis. Through a detailed family history the pediatrician can often ascertain the mode of genetic transmission and the risks to family members. Because not all familial clustering of disease is caused by genetic factors, a family history can also identify common environmental and behavioral factors that influence the occurrence of disease. The main goal of the family history is to identify genetic susceptibility, and the cornerstone of the family history is a systematic and standardized pedigree.

A pedigree provides a graphic depiction of a family’s structure and medical history. It is important when taking a pedigree to be systematic and use standard symbols and configurations (Figs. 80-1 to 80-4) so that anyone can read and understand the information. In the pediatric setting, the proband is typically the child or adolescent who is being evaluated. The proband is designated in the pedigree by an arrow. A 3 to 4-generation pedigree should be obtained for every new patient as an initial screen for genetic disorders segregating within the family. The pedigree can provide clues to the inheritance pattern of these disorders and can aid the clinician in determining the risk to the proband and other family members. The closer the relationship of the proband to the person in the family with the genetic disorder, the greater is the shared genetic complement. First-degree relatives, such as a parent, full sibling, or child, share \( \frac{1}{2} \) their genetic information on average; first cousins share \( \frac{1}{4} \). Sometimes the person providing the family history may mention a distant relative who is affected with a genetic disorder. In such cases a more extensive pedigree may be needed to identify the risk to other family members. For example, a history of a distant maternally related cousin with mental retardation caused by fragile X syndrome can still place a male proband at an elevated risk for this disorder.

MENDELIAN INHERITANCE
There are 3 classic forms of genetic inheritance: autosomal dominant, autosomal recessive, and X-linked. These are referred to as mendelian inheritance forms, after Gregor Mendel, the 19th-century monk whose experiments led to the laws of segregation of characteristics, dominance, and independent assortment. These remain the foundation of single-gene inheritance.

Autosomal Dominant Inheritance
Autosomal dominant inheritance is determined by the presence of 1 abnormal gene on 1 of the autosomes (chromosomes 1-22). Autosomal genes exist in pairs, with each parent contributing 1 copy. In an autosomal dominant trait, a change in 1 of the paired genes has an effect on the phenotype; this can refer to physical manifestations, behavioral characteristics, or differences detectable only through laboratory tests, even though the other copy of the gene is functioning correctly.

The pedigree for an autosomal dominant disorder (Fig. 80-5) demonstrates certain characteristics. The disorder is transmitted in a vertical (parent-to-child) pattern and can appear in multiple generations. This is illustrated by individual I.1 (see Fig. 80-5) passing on the changed gene to II.2 and II.5. An affected individual has a 50% (1 in 2) chance of passing on the deleterious gene in each pregnancy and, therefore, of having a child affected by the disorder. This is referred to as the recurrence risk for the disorder. Unaffected individuals (family members who do not manifest the trait) do not pass the disorder to their children. Males and females are equally affected. Although not a characteristic per se, the finding of male-to-male transmission essentially confirms autosomal dominant inheritance. Vertical transmission can also be seen with X-linked traits. However, because a father passes his Y chromosome to a son, male-to-male transmission cannot be seen with an X-linked trait. Therefore, male-to-male transmission eliminates X-linked inheritance as a possible explanation. Although male-to-male transmission can occur with Y-linked genes as well, there are very few Y-linked disorders compared with thousands having the autosomal dominant inheritance pattern.

Although parent-to-child transmission is a characteristic of autosomal dominant inheritance, for many patients with an autosomal dominant disorder there is no history of an affected family member. There are several possible reasons: First, the patient may represent a new mutation that occurred in the DNA of the egg or sperm that came together to form that individual. Second, many autosomal dominant conditions demonstrate incomplete penetrance, meaning that not all individuals who carry the mutation have phenotypic manifestations. In a pedigree this can appear as a skipped generation, in which an
Instructions:
— Key should contain all information relevant to interpretation of pedigree (e.g., define fill/shading)
— For clinical (non-published) pedigrees include:
  a) name of proband/consultand
  b) family names/initiais of relatives for identification, as appropriate
  c) name and title of person recording pedigree
  d) historian (person relaying family history information)
  e) date of intake/update
  f) reason for taking pedigree (e.g., abnormal ultrasound, familial cancer, developmental delay, etc.)
  g) ancestry of both sides of family
— Recommended order of information placed below symbol (or to lower right)
  a) age; can note year of birth (e.g., b. 1978) and/or death (e.g., d. 2007)
  b) evaluation (see Figure 75-4)
  c) pedigree number (e.g., I-1, I-2, I-3)
— Limit identifying information to maintain confidentiality and privacy

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</tr>
<tr>
<td>2. Affected individual</td>
<td></td>
<td></td>
<td></td>
<td>Key/legend used to define shading or other fill (e.g., hatches, dots, etc.). Use only when individual is clinically affected.</td>
</tr>
<tr>
<td>3. Multiple individuals, number known</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>Number of siblings written inside symbol. (Affected individuals should not be grouped.)</td>
</tr>
<tr>
<td>4. Multiple individuals, number unknown or unstated</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>“n” used in place of “?”:</td>
</tr>
<tr>
<td>5. Deceased individual</td>
<td></td>
<td></td>
<td></td>
<td>Indicate cause of death if known. Do not use a cross (†) to indicate death to avoid confusion with evaluation positive (+).</td>
</tr>
<tr>
<td>6. Consultand</td>
<td></td>
<td></td>
<td></td>
<td>Individual(s) seeking genetic counseling/testing.</td>
</tr>
<tr>
<td>7. Proband</td>
<td></td>
<td></td>
<td></td>
<td>An affected family member coming to medical attention independent of other family members.</td>
</tr>
<tr>
<td>8. Stillbirth (SB)</td>
<td></td>
<td></td>
<td></td>
<td>Include gestational age and karyotype, if known.</td>
</tr>
<tr>
<td>9. Pregnancy (P)</td>
<td></td>
<td></td>
<td></td>
<td>Gestational age and karyotype below symbol. Light shading can be used for affected; define in key/legend.</td>
</tr>
</tbody>
</table>

Pregnancies not carried to term

<table>
<thead>
<tr>
<th></th>
<th>Affected</th>
<th>Unaffected</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>10. Spontaneous abortion (SAB)</td>
<td>17 wks female cystic hygroma</td>
<td>&lt;10 wks</td>
<td>If gestational age/gender known, write below symbol. Key/legend used to define shading.</td>
</tr>
<tr>
<td>11. Termination of pregnancy (TOP)</td>
<td>18 wks</td>
<td>47, XY = 18</td>
<td>Other abbreviations (e.g., TAB, VTOP) not used for sake of consistency.</td>
</tr>
<tr>
<td>12. Ectopic pregnancy (ECT)</td>
<td>ECT</td>
<td></td>
<td>Write ECT below symbol.</td>
</tr>
</tbody>
</table>

Figure 80-1 Common pedigree symbols, definitions, and abbreviations. (From Bennett RL, French KS, Resta RG, et al: Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors, J Genet Couns 17:424–433, 2008.)

unaffected individual links 2 affected persons (Fig. 80-6). There are many potential reasons that a disorder exhibits incomplete penetrance, including the effect of modifier genes, environmental factors, gender, and age. Third, individuals with the same autosomal dominant mutation can manifest the disorder to different degrees. This is termed variable expression and is a characteristic of many autosomal dominant disorders. Fourth, some spontaneous genetic mutations occur not in the egg or sperm that forms a child, but rather in a cell in the developing embryo. Such events are referred to as somatic mutations, and because not all cells are affected, the change is said to be mosaic. The
affected, although some traits exhibit different expression in males and females and increased incidence, particularly for rare traits, in the offspring of consanguineous parents. Consanguinity refers to the existence of a relationship by a common ancestor and increases the chance that both parents carry a gene affected by an identical mutation that they inherited. Consanguinity between parents of a child with a suspected genetic disorder implies (but does not prove) autosomal recessive inheritance. Although consanguineous unions are uncommon in Western society, in other parts of the world (southern India, Japan, and the Middle East) they are common; the incidence may be as high as 50%. The risk of a genetic disorder for the offspring of a first-cousin marriage (6-8%) is about double the risk in the general population (3-4%).

Every individual probably has several rare, harmful, recessive mutations. Because most mutations carried in the general population occur.

**Figure 80-2 Pedigree line definitions.** (From Bennett RL, French KS, Resta RG, et al: Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors, J Genet Couns 17:424–433, 2008.)
at a very low frequency, it does not make economic sense to screen the entire population in order to identify the small number of persons who carry these mutations. As a result, these mutations typically remain undetected unless an affected child is born to a couple who both carry mutations affecting the same gene.

However, in some genetic isolates (small populations separated by geography, religion, culture, or language) certain rare recessive mutations are far more common than in the general population. Even though there may be no known consanguinity, couples from these genetic isolates have a greater chance of sharing mutant alleles inherited from a common ancestor. Screening programs have been developed among some such groups to detect persons who carry common disease-causing mutations and therefore are at increased risk for having affected children. For example, a variety of autosomal recessive conditions are more common among Ashkenazi Jews than in the general population. Couples of Ashkenazi Jewish ancestry should be offered prenatal or preconception screening for Gaucher disease type 1 (carrier rate 1:14), cystic fibrosis (1:25), Tay-Sachs disease (1:25), familial dysautonomia (1:30), Canavan disease (1:40), glycogen storage disease type 1A (1:71), maple syrup urine disease (1:81), Fanconi anemia type C (1:89), Niemann-Pick disease type A (1:90), Bloom syndrome (1:100), mucolipidosis IV (1:120), and possibly neonatal familial hyperinsulinemic hypoglycemia.

The prevalence of carriers of certain autosomal recessive genes in some larger populations is unusually high. In such cases, heterozygote advantage is postulated. For example, the carrier frequencies of sickle cell disease in the African population and of cystic fibrosis in the northern European population are much higher than would be expected from new mutations. It is possible that heterozygous carriers have had an advantage in terms of survival and reproduction over
Figure 80-4 Pedigree symbols of genetic evaluation and testing information. (From Bennett RL, French KS, Resta RG, et al: Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors, J Genet Couns 17:424–433, 2008.)

**Instructions:**
- E is used for evaluation to represent clinical and/or test information on the pedigree
  - E is to be defined in key/legend
  - If more than one evaluation, use subscript (E₁, E₂, E₃) and define in key
  - Test results should be put in parentheses or defined in key/legend
- A symbol is shaded only when an individual is clinically symptomatic
- For linkage studies, haplotype information is written below the individual. The haplotype of interest should be on left and appropriately highlighted
- Repetitive sequences, trinucleotides, and expansion numbers are written with affected allele first and placed in parentheses
- If mutation known, identify in parentheses

<table>
<thead>
<tr>
<th>Definition</th>
<th>Symbol</th>
<th>Scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Documented evaluation (*)</td>
<td>*</td>
<td>Woman with negative echocardiogram.</td>
</tr>
<tr>
<td>Use only if examined/evaluated by you or your research/clinical team or if the outside evaluation has been reviewed and verified.</td>
<td></td>
<td>E⁻ (echo)</td>
</tr>
<tr>
<td>2. Carrier—not likely to manifest disease regardless of inheritance pattern</td>
<td>□</td>
<td>Male carrier of Tay-Sachs disease by patient report (*) not used because results not verified.</td>
</tr>
<tr>
<td>3. Asymptomatic/presymptomatic carrier—clinically unaffected at this time but could later exhibit symptoms</td>
<td>□</td>
<td>Woman age 25 with negative mammogram and positive BRCA1 DNA test.</td>
</tr>
<tr>
<td></td>
<td>25 y</td>
<td>E₁⁻ (mammogram) E₂⁺ (5385insC BRCA1)</td>
</tr>
<tr>
<td>4. Uninformative study (u)</td>
<td>Eu</td>
<td>Man age 25 with normal physical exam and uninformative DNA test for Huntington disease (E₂).</td>
</tr>
<tr>
<td></td>
<td>25 y</td>
<td>E₁⁻ (physical exam) E₃u (36n/18n)</td>
</tr>
<tr>
<td>5. Affected individual with positive evaluation (E⁺)</td>
<td>E⁺</td>
<td>Individual with cystic fibrosis and positive mutation study; only one mutation has currently been identified.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 week male fetus with a trisomy 18 karyotype.</td>
</tr>
</tbody>
</table>

**Figure 80-5 Autosomal dominant pedigree.** Pedigree showing typical inheritance of a form of achondroplasia (FGFR3) inherited as an autosomal dominant trait. Black, affected patients.

**Figure 80-6 Incomplete penetrance.** This family segregates a familial cancer syndrome, familial adenomatous polyposis. Individual II.3 is an obligate carrier, but there are no findings to suggest the disorder. This disorder is nonpenetrant in this individual.
noncarriers. In sickle cell disease, the carrier state might confer some resistance to malaria; in cystic fibrosis, the carrier state has been postulated to confer resistance to cholera or enteropathogenic *Escherichia coli* infections. Population-based carrier screening for cystic fibrosis is recommended for persons of northern European and Ashkenazi Jewish ancestry; population-based screening for sickle cell disease is recommended for persons of African ancestry.

If the frequency of an autosomal recessive disease is known, the frequency of the heterozygote or carrier state can be calculated from the Hardy-Weinberg formula:

\[
p^2 + 2pq + q^2 = 1
\]

where \( p \) is the frequency of one of a pair of alleles and \( q \) is the frequency of the other. For example, if the frequency of cystic fibrosis among white Americans is 1 in 2,500 (\( p^2 \)), then the frequency of the heterozygote (2pq) can be calculated: If \( p^2 = 1/2,500 \), then \( p = 1/50 \) and \( q = 49/50; 2pq = 2 \times (1/50) \times (49/50) = 98/2500 \) or 3.92%.

**Pseudodominant Inheritance**

Pseudodominant inheritance refers to the observation of apparent dominant (parent to child) transmission of a known autosomal recessive disorder (Fig. 80-8). This occurs when a homozygous affected individual has a partner who is a heterozygous carrier, and it is most likely to occur for relatively common traits, such as sickle cell anemia or nonsyndromic autosomal recessive hearing loss because of mutations in *GJB2*, the gene that encodes Connexin 26.

**X-Linked Inheritance**

Characteristics of X-linked inheritance (Fig. 80-9) include the following:

- Males are more commonly and more severely affected than females.
- Female carriers are generally unaffected, or if affected, they are affected more mildly than males.
- Female carriers have a 25% risk for having an affected son, a 25% risk for a carrier daughter, and a 50% chance of having a child that does not inherit the mutated X-linked gene.
- Affected males have carrier daughters and unaffected sons because they pass their X chromosome to all of their daughters and their Y chromosome to all of their sons. Male-to-male transmission excludes X-linkage but is seen with autosomal dominant and Y-linked inheritance.

A female occasionally exhibits signs of an X-linked trait similar to a male. This occurs rarely owing to homozygosity for an X-linked trait or the presence of a sex chromosome abnormality (45,X or 46,XY female) or skewed or nonrandom X-inactivation. X chromosome inactivation occurs early in development and involves random and irreversible inactivation of most genes on one X chromosome in female cells (Fig. 80-10). In some cases, a preponderance of cells inactivates the same X chromosome, resulting in phenotypic expression of an X-linked mutation if it resides on the active chromosome. This can occur owing to chance, selection against cells that have inactivated the X chromosome carrying the normal gene, or X chromosome abnormalities that result in inactivation of the X chromosome carrying the normal gene.

Some X-linked disorders are inherited in an X-linked dominant fashion in which female carriers typically manifest abnormal findings. An affected man will have only affected daughters and unaffected sons, and half of the offspring of an affected woman will be affected (Fig. 80-11). Some X-linked dominant conditions are lethal in a high percentage of males. An example is incontinentia pigmenti (see Chapter 596.7). The pedigree shows only affected females and an overall ratio of 2:1 females to males with an increased number of miscarriages (Fig. 80-12).

**Y-LINKED INHERITANCE**

There are few Y-linked traits. These demonstrate only male-to-male transmission, and only males are affected (Fig. 80-13). Most Y-linked genes are related to male sex determination and reproduction and are associated with infertility. Therefore, it is rare to see familial transmission of a Y-linked disorder. However, advances in assisted reproductive technologies might make it possible to have familial transmission of male infertility.

Of special note are the pseudoautosomal regions on the Y chromosome that have homology that is shared by both Xp and Yp. Very few genes reside in this region. One of the few is *SHOX*. Heterozygous *SHOX* mutations cause Leri-Weil dyschondrosteosis, a rare skeletal dysplasia that involves bilateral bowing of the forearms with
dislocations of the ulna at the wrist and generalized short stature. Homozygous mutations cause the much more severe Langer mesomelic dwarfism.

DIGENIC INHERITANCE

Digenic inheritance explains the occurrence of retinitis pigmentosa (RP) in children of parents who each carry a mutation in a different RP-associated gene. Both parents have normal vision, as would be expected, but their offspring who are double heterozygotes—having inherited both mutations—develop RP. Digenic pedigrees (Fig. 80-14) can exhibit characteristics of both autosomal dominant (vertical transmission) and autosomal recessive inheritance (1 in 4 recurrence risk). For example, a couple in which the 2 unaffected partners are carriers for mutation in 2 different RP-associated genes that show digenic inheritance have a 1 in 4 risk of having an affected child similar to what is seen in autosomal recessive inheritance. However, their affected

Figure 80-10 X-inactivation. Black marks the active X chromosome. Color of the cell represents its active X chromosome is paternally (X_p, blue) or maternally (X_m, pink) derived.

Figure 80-11 Pedigree pattern demonstrating X-linked dominant inheritance. Note there is no father-to-son transmission in this situation, and hemizygosity (i.e., X-linked gene in a male) is not lethal. In some X-linked dominant conditions, X-linked males have a more severe phenotype and might not survive. In that case, only females manifest the disease (see Fig. 80-12).

Figure 80-12 Pedigree of an X-linked dominant disorder with male lethality, such as incontinentia pigmenti.

Figure 80-13 Y-linked inheritance. Black, affected patient.
Part X

Human Genetics

**Figure 80-14 Digenic pedigree.** Here, the disease alleles are a and b and they reside on distinct genetic loci or genes. For a person to have the disease, heterozygosity for mutant alleles in both genes (A/a;B/b) is required.

![Digenic Pedigree](image)

children, and affected children in subsequent generations, have a 1 in 4 risk of transmitting both mutations to their offspring, who would be affected (vertical transmission).

**PSEUDOGENETIC INHERITANCE AND FAMILIAL CLUSTERING**

Sometimes nongenetic reasons for the occurrence of a particular disease in multiple family members can produce a pattern that mimics genetic transmission. These nongenetic factors can include identifiable environmental factors, teratogenic exposures, or as yet undefined factors. Examples of identifiable factors might include multiple siblings in a family having asthma as a result of exposure to cigarette smoke from their parents or having failure to thrive, developmental delay, and unusual facial appearance caused by exposure to alcohol during pregnancy.

In some cases the disease is sufficiently common in the general population that some familial clustering occurs simply by chance. Breast cancer affects 11% of all women, and it is possible that several women in a family will develop breast cancer even in the absence of a genetic predisposition. However, hereditary breast cancer associated with mutations in BRCA1 and BRCA2 should be suspected in any individual who has a personal history of breast cancer with onset before age 50 yr, early-onset breast and ovarian cancer at any age, bilateral or multifocal breast cancer, a family history of breast cancer or breast and ovarian cancer consistent with autosomal dominant inheritance, and/or a personal or family history of male breast cancer.

**NONTRADITIONAL INHERITANCE**

Some genetic disorders are inherited in a manner that does not follow classical Mendelian patterns. Nontraditional inheritance includes mitochondrial disorders, triplet repeat expansion diseases, and imprinting defects.

**Mitochondrial Inheritance**

An individual's mitochondrial genome is entirely derived from the mother because sperm contain few mitochondria, which are typically shed upon fertilization. It follows that mitochondrial disorders exhibit maternal inheritance. A woman with a mitochondrial genetic disorder can have affected offspring of either sex, but an affected father cannot pass on the disease to his offspring (Fig. 80-15). Mitochondrial DNA mutations are often deletions or point mutations; overall, 1:400 people has a maternally inherited pathogenic mitochondrial DNA mutation.

In individual families, mitochondrial inheritance may be difficult to distinguish from autosomal dominant or X-linked inheritance, but in many cases, paying close attention to the sex of the transmit-

ting and nontransmitting parents can suggest a mitochondrial basis (Table 80-1).

The mitochondria are the cell's suppliers of energy, and it is not surprising that the organs that are most affected by the presence of abnormal mitochondria are those that have the greatest energy requirements, such as the brain, muscle, heart, and liver (see Chapters 87.4, 361, 598.2, and 611.4). Common manifestations include developmental delay, seizures, cardiac dysfunction, decreased muscle strength and tone, and hearing and vision problems. Examples of mitochondrial disorders include MELAS (myopathy, encephalopathy, lactic acidosis, and strokelike episodes), MERRF (myoclonic epilepsy associated with ragged red fibers), and Kearns-Sayre syndrome (ophthalmoplegia, pigmentary retinopathy, and cardiomyopathy) (see Chapter 598.2 and 611.4).

Mitochondrial diseases can be highly variable in clinical manifestation. This is partly because cells can contain multiple mitochondria, each bearing several copies of the mitochondrial genome. Thus, a cell can have a mixture of normal and abnormal mitochondrial genomes, which is referred to as heteroplasmasy. Unequal segregation of mitochondria carrying normal and abnormal genomes and replicative advantage can result in varying degrees of heteroplasmasy in the cells of an affected individual, including the individual ova of an affected female. Because of this, a mother may be asymptomatic and yet have children who are severely affected. The level of heteroplasmasy at which disease symptoms typically appear can also vary based on the type of mitochondrial mutation. Detection of mitochondrial genome mutations can require sampling of the affected tissue for DNA analysis; testing for mitochondrial DNA mutations may in some tissues, such as blood, be inadequate because the mutation may be found primarily in affected tissues such as muscle.

**Triplet Repeat Expansion Disorders**

Triplet repeat expansion disorders are distinguished by the special dynamic nature of the disease-causing mutation. Triplet repeat expansion disorders include fragile X syndrome, myotonic dystrophy, Huntington disease, spinocerebellar ataxias, and several others (Table 80-2). These disorders are caused by expansion in the number of 3-bp repeats. The fragile X gene, FMR1, normally has 5-40 CGG triplets. An error in replication can result in expansion of that number to a level in the gray zone between 41 and 58 repeats, or to a level referred to as premutation, which comprises 59-200 repeats. Some male carriers of the premutation develop fragile X-associated tremor/ataxia syndrome (FXTAS) as adults, and female carriers of the premutation are at risk for fragile X-associated primary ovarian insufficiency (FXPOI). Persons with a premutation are also at risk for having the gene expand further in subsequent meiosis, hence crossing into the range of full mutation in offspring. In fragile X, the threshold for clinical diagnosis is above 200 repeats. With this number of repeats, the FMR1 gene becomes hypermethylated, and protein production is lost.

Some triplet expansions associated with other genes can cause disease through a mechanism other than decreased protein production. In Huntington disease, the expansion causes the gene product...
### Table 80-1: Representative Examples of Disorders Caused by Mutations in Mitochondrial DNA and Their Inheritance

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>PHENOTYPE</th>
<th>MOST FREQUENT MUTATION IN MTDNA MOLECULE</th>
<th>HOMOPLASMY VS. HETEROPLASMY</th>
<th>INHERITANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leber hereditary optic neuropathy</td>
<td>Rapid optic nerve death, leading to blindness in young adult life</td>
<td>Substitution Arg340His in ND1 gene of complex I of electron transport chain; other complex I missense mutations</td>
<td>Homoplasmic (usually)</td>
<td>Maternal</td>
</tr>
<tr>
<td>NARP, Leigh disease</td>
<td>Neuropathy, ataxia, retinitis pigmentosa, developmental delay, mental retardation, lactic acidemia</td>
<td>Point mutations in ATPase subunit 6 gene</td>
<td>Heteroplasmic</td>
<td>Maternal</td>
</tr>
<tr>
<td>MELAS</td>
<td>Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; may manifest only as diabetes mellitus</td>
<td>Point mutation in tRNA&lt;sup&gt;Leu&lt;/sup&gt;</td>
<td>Heteroplasmic</td>
<td>Maternal</td>
</tr>
<tr>
<td>MERRF</td>
<td>Myoclonic epilepsy, ragged red fibers in muscle, ataxia, sensorineural deafness</td>
<td>Point mutation in tRNA&lt;sup&gt;Lys&lt;/sup&gt;</td>
<td>Heteroplasmic</td>
<td>Maternal</td>
</tr>
<tr>
<td>Deafness</td>
<td>Progressive sensorineural deafness, often induced by aminoglycoside antibiotics</td>
<td>A1555G mutation in 12S rRNA</td>
<td>Homoplasmic</td>
<td>Maternal</td>
</tr>
<tr>
<td>Chronic progressive external ophthalmoplegia (CPEO)</td>
<td>Progressive weakness of extraocular muscles</td>
<td>The common MELAS point mutation in tRNA&lt;sup&gt;Leu&lt;/sup&gt;; large deletions similar to KSS</td>
<td>Heteroplasmic Maternal if point mutations</td>
<td>Slight Heteroplasmic Sporadic, somatic mutations</td>
</tr>
<tr>
<td>Pearson syndrome</td>
<td>Pancreatic insufficiency, pancytopenia, lactic acidosis</td>
<td>Large deletions</td>
<td>Heteroplasmic</td>
<td>Slight Heteroplasmic Sporadic, somatic mutations</td>
</tr>
<tr>
<td>Kearns-Sayre syndrome (KSS)</td>
<td>PEO of early onset with heart block, retinal pigmentation</td>
<td>5 kb large deletion</td>
<td>Heteroplasmic</td>
<td>Slight Heteroplasmic Sporadic, somatic mutations</td>
</tr>
</tbody>
</table>

mtDNA, Mitochondrial DNA; rRNA, ribosomal RNA; tRNA, transfer RNA.


### Table 80-2: Diseases Associated with Polynucleotide Repeat Expansions

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>DESCRIPTION</th>
<th>REPEAT SEQUENCE</th>
<th>NORMAL RANGE</th>
<th>ABNORMAL RANGE</th>
<th>PARENT IN WHOM EXPANSION USUALLY OCCURS</th>
<th>LOCATION OF EXPANSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>CATEGORY 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huntington disease</td>
<td>Loss of motor control, dementia, affective disorder</td>
<td>CAG</td>
<td>6-34</td>
<td>36-100 or more</td>
<td>More often through father</td>
<td>Exon</td>
</tr>
<tr>
<td>Spinal and bulbar muscular atrophy</td>
<td>Adult-onset motor-neuron disease associated with androgen insensitivity</td>
<td>CAG</td>
<td>11-34</td>
<td>40-62</td>
<td>More often through father</td>
<td>Exon</td>
</tr>
<tr>
<td>Spinocerebellar ataxia type 1</td>
<td>Progressive ataxia, dysarthria, dystrophia</td>
<td>CAG</td>
<td>6-39</td>
<td>41-81</td>
<td>More often through father</td>
<td>Exon</td>
</tr>
<tr>
<td>Spinocerebellar ataxia type 2</td>
<td>Progressive ataxia, dysarthria</td>
<td>CAG</td>
<td>15-29</td>
<td>35-59</td>
<td></td>
<td>Exon</td>
</tr>
<tr>
<td>Spinocerebellar ataxia type 3</td>
<td>Dystonia, distal muscular atrophy, ataxia, external ophthalmoplegia</td>
<td>CAG</td>
<td>13-36</td>
<td>68-79</td>
<td>More often through father</td>
<td>Exon</td>
</tr>
<tr>
<td>Spinocerebellar ataxia type 6</td>
<td>Progressive ataxia, dysarthria, nystagmus</td>
<td>CAG</td>
<td>4-16</td>
<td>21-27</td>
<td></td>
<td>Exon</td>
</tr>
<tr>
<td>Spinocerebellar ataxia type 7</td>
<td>Progressive ataxia, dysarthria, retinal degeneration</td>
<td>CAG</td>
<td>7-35</td>
<td>38-200</td>
<td>More often through father</td>
<td>Exon</td>
</tr>
<tr>
<td>Spinocerebellar ataxia type 17</td>
<td>Progressive ataxia, dementia, bradykinasia, dysmetria</td>
<td>CAG</td>
<td>29-42</td>
<td>47-55</td>
<td></td>
<td>Exon</td>
</tr>
<tr>
<td>Dentatorubral-pallidoluysian atrophy/Haw River syndrome</td>
<td>Cerebellar atrophy, ataxia, myoclonic epilepsy, choreoathetosis, dementia</td>
<td>CAG</td>
<td>7-25</td>
<td>49-88</td>
<td>More often through father</td>
<td>Exon</td>
</tr>
</tbody>
</table>

*Continued*
to have a new, toxic effect on the neurons of the basal ganglia. For most triplet-repeat disorders, there is a clinical correlation to the size of the expansion, with a greater expansion causing more severe symptoms and/or earlier age of onset for the disease. The observation of increasing severity of disease and early age at onset in subsequent generations is termed genetic anticipation and is a defining characteristic of many triplet-repeat expansion disorders (Fig. 80-16).

**Genetic Imprinting**

The 2 copies of most autosomal genes are functionally equivalent. However, in some cases only 1 copy of a gene is transcribed and the other copy is silenced. This gene silencing is typically associated with methylation of DNA, which is an epigenetic modification, meaning it does not change the nucleotide sequence of the DNA (Fig. 80-17). In imprinting, gene expression depends on the parent of origin of the chromosome (see Chapter 81.8). Imprinting disorders result from an imbalance of active copies of a given gene, which can occur for several reasons. Prader-Willi and Angelman syndromes, two distinct disorders associated with developmental impairment, are illustrative. Both

---

**Table 80-2  Diseases Associated with Polynucleotide Repeat Expansions—cont’d**

<table>
<thead>
<tr>
<th>CATEGORY 2</th>
<th>DISEASE</th>
<th>DESCRIPTION</th>
<th>REPEAT SEQUENCE</th>
<th>NORMAL RANGE</th>
<th>ABNORMAL RANGE</th>
<th>PARENT IN WHOM EXPANSION USUALLY OCCURS</th>
<th>LOCATION OF EXPANSION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pseudoachondroplasia, multiple epiphyseal dysplasia</td>
<td>Short stature, joint laxity, degenerative joint disease</td>
<td>GAC</td>
<td>5</td>
<td>6-7</td>
<td>—</td>
<td>Exon</td>
</tr>
<tr>
<td></td>
<td>Oculopharyngeal muscular dystrophy</td>
<td>Proximal limb weakness, dysphagia, ptosis</td>
<td>GCG</td>
<td>6</td>
<td>7-13</td>
<td>—</td>
<td>Exon</td>
</tr>
<tr>
<td></td>
<td>Cleidocranial dysplasia</td>
<td>Short stature, open skull sutures with bulging calvaria, clavicular hypoplasia, shortened fingers, dental anomalies</td>
<td>GCC, GCT, GCA</td>
<td>17</td>
<td>27 (expansion observed in 1 family)</td>
<td>—</td>
<td>Exon</td>
</tr>
<tr>
<td></td>
<td>Synpolydactyly</td>
<td>Polydactyly and syndactyly</td>
<td>GCC, GCT, GCA</td>
<td>15</td>
<td>22-25</td>
<td>—</td>
<td>Exon</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CATEGORY 3</th>
<th>DISEASE</th>
<th>DESCRIPTION</th>
<th>REPEAT SEQUENCE</th>
<th>NORMAL RANGE</th>
<th>ABNORMAL RANGE</th>
<th>PARENT IN WHOM EXPANSION USUALLY OCCURS</th>
<th>LOCATION OF EXPANSION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Myotonic dystrophy (DM1; chromosome 19)</td>
<td>Muscle loss, cardiac arrhythmia, cataracts, frontal balding</td>
<td>CTG</td>
<td>5-37</td>
<td>100 to several thousand</td>
<td>Either parent, but expansion to congenital form through mother</td>
<td>3' untranslated region</td>
</tr>
<tr>
<td></td>
<td>Myotonic dystrophy (DM2; chromosome 3)</td>
<td>Muscle loss, cardiac arrhythmia, cataracts, frontal balding</td>
<td>CCTG</td>
<td>&lt;75</td>
<td>75-11,000</td>
<td>—</td>
<td>3' untranslated region</td>
</tr>
<tr>
<td></td>
<td>Friedreich ataxia</td>
<td>Progressive limb ataxia, dystartha, hypertrophic cardiomyopathy, pyramidal weakness in legs</td>
<td>GAA</td>
<td>7-2</td>
<td>200-900 or more</td>
<td>Autosomal recessive inheritance, so disease alleles are inherited from both parents</td>
<td>Intron</td>
</tr>
<tr>
<td></td>
<td>Fragile X syndrome (FRAXA)</td>
<td>Mental retardation, large ears and jaws, macroorchidism in males</td>
<td>CGG</td>
<td>6-52</td>
<td>200-2,000 or more</td>
<td>Exclusively through mother</td>
<td>5' untranslated region</td>
</tr>
<tr>
<td></td>
<td>Fragile site (FRAXE)</td>
<td>Mild mental retardation</td>
<td>GCC</td>
<td>6-35</td>
<td>&gt;200</td>
<td>More often through mother</td>
<td>5' untranslated region</td>
</tr>
<tr>
<td></td>
<td>Spinocerebellar ataxia type 8</td>
<td>Adult-onset ataxia, dysartha, nystagmus</td>
<td>CTG</td>
<td>16-37</td>
<td>107-127</td>
<td>More often through mother</td>
<td>3' untranslated region</td>
</tr>
<tr>
<td></td>
<td>Spinocerebellar ataxia type 10</td>
<td>Ataxia and seizures</td>
<td>ATTCT</td>
<td>12-16</td>
<td>800-4,500</td>
<td>More often through father</td>
<td>Intron</td>
</tr>
<tr>
<td></td>
<td>Spinocerebellar ataxia type 12</td>
<td>Ataxia, eye movement disorders; variable age at onset</td>
<td>CAG</td>
<td>7-28</td>
<td>66-78</td>
<td>—</td>
<td>5' untranslated region</td>
</tr>
<tr>
<td></td>
<td>Progressive myoclonic epilepsy type 1</td>
<td>Juvenile-onset convulsions, myoclonus, dementia</td>
<td>12-bp repeat motif</td>
<td>2-3</td>
<td>30-75</td>
<td>Autosomal recessive inheritance, so transmitted by both parents</td>
<td>5' untranslated region</td>
</tr>
</tbody>
</table>

Patterns of Genetic Transmission

DNA methylation patterns within a cell are characteristic of that cell type. Cell type-specific and tissue-specific DNA methylation are illustrated by organ-to-organ variations in the clusters of methylated CpGs within the same individual. Despite overall consistency in tissue-specific DNA methylation patterns, variations in these patterns exist among different individuals. Methylated CpGs are indicated by a filled circle and unmethylated CpGs by an open circle. SNPs are indicated by the corresponding base. (Redrawn from Brena RM, Huang THM, Plass C: Toward a human epigenome, Nat Genet 38:1359–1360, 2006.)

Multifactorial inheritance refers to traits that are caused by a combination of inherited, environmental, and stochastic factors. There is a similar rate of recurrence among all 1st-degree relatives (parents, siblings, offspring of the affected child). It is unusual to find a substantial increase in risk for relatives related more distantly than 2nd degree to the index case. The risk of recurrence is related to the incidence of the disease. Some disorders have a sex predilection, as indicated by an unequal male:female incidence. Pyloric stenosis, for example, is more common in males, whereas congenital dislocation of the hips is more common in females. Where there is an altered sex ratio, the risk is higher for the relatives of an index case whose gender is less commonly affected than relatives of an index case of the more commonly affected gender. For example, the risk to the son of an affected female is 20%, compared with the 5% risk for the son of an affected male.

Multifactorial traits differ from polygenic inheritance, which refers to traits that result from the additive effects of multiple genes. Multifactorial traits segregate within families but do not exhibit a consistent or recognizable inheritance pattern. Characteristics include the following:

- There is a similar rate of recurrence among all 1st-degree relatives (parents, siblings, offspring of the affected child). It is unusual to find a substantial increase in risk for relatives related more distantly than 2nd degree to the index case.
- The risk of recurrence is related to the incidence of the disease.
- Some disorders have a sex predilection, as indicated by an unequal male:female incidence. Pyloric stenosis, for example, is more common in males, whereas congenital dislocation of the hips is more common in females. Where there is an altered sex ratio, the risk is higher for the relatives of an index case whose gender is less commonly affected than relatives of an index case of the more commonly affected gender. For example, the risk to the son of an affected female with infantile pyloric stenosis is 18%, compared with the 5% risk for the son of an affected male. An affected female presumably has a greater genetic susceptibility, which she can then pass on to her offspring.
- The likelihood that both identical twins will be affected with the same malformation is less than 100% but much greater than the chance that both members of a nonidentical twin pair will be affected. This is in contrast with the pattern seen in mendelian...
inheritance, in which identical twins almost always share fully penetrant genetic disorders.

- The risk of recurrence is increased when multiple family members are affected. A simple example is that the risk of recurrence for unilateral cleft lip and palate is 4% for a couple with 1 affected child and increases to 9% with 2 affected children. It is sometimes difficult to distinguish between a multifactorial and mendelian etiology in families with multiple affected individuals.

- The risk of recurrence may be greater when the disorder is more severe. For example, an infant who has long-segment Hirschsprung disease has a greater chance of having an affected sibling than the infant who has short-segment Hirschsprung disease.

There are 2 types of multifactorial traits. One exhibits continuous variation, with “normal” individuals falling within a statistical range—often defined as having a value 2 SDs above and/or below the mean—and “abnormals” falling outside that range. Examples include such traits as intelligence, blood pressure, height, and head circumference. For many of these traits, offspring values can be estimated based on a modified average of their parental values, with nutritional and environmental factors playing an important role.

With other multifactorial traits, the distinction between normal and abnormal is based on the presence or absence of a particular trait. Examples include pyloric stenosis, neural tube defects, congenital heart defects, and cleft lip and cleft palate. Such traits follow a threshold model (see Fig. 80-15). A distribution of liability because of genetic and nongenetic factors is postulated in the population. Individuals who exceed a threshold liability develop the trait, and those below the threshold do not.

The balance between genetic and environmental factors is demonstrated by neural tube defects. Genetic factors are implicated by the increased recurrence risk for parents of an affected child compared with the general population, yet the recurrence risk is about 3%, less than what would be expected if the trait was caused by a single, fully penetrant mutation. The role of nongenetic environmental factors can be seen in the fact that the recurrence risk can be lowered by up to 87% if the mother-to-be takes 4 mg of folic acid per day starting 3 mo before conception.

Many adult-onset diseases behave as if they are caused by multifactorial inheritance. Diabetes, coronary artery disease, and schizophrenia are examples.

Figure 80-18 The progressive decrease in the genetic load contributing to the development of a disease creates a smooth transition in the distribution of illnesses on an etiologic diagram. In theory, no diseases are completely free from the influence of both genetic and environmental factors. (From Bomprezzi R, Kovanen PE, Martin R: New approaches to investigating heterogeneity in complex traits, J Med Genet 40:553–559, 2003. Reproduced with permission from the BMJ Publishing Group.)

Bibliography is available at Expert Consult.


Clinical cytogenetics is the study of chromosomes: their structure, function, inheritance, and abnormalities. Chromosome abnormalities are very common and occur in approximately 1-2% of live births, 5% of stillbirths, and 50% of early fetal losses in the 1st trimester of pregnancy (Table 81-1). Chromosome abnormalities are more common among persons with intellectual disability and they play a significant role in the development of some neoplasias.

Chromosome analyses are indicated in persons presenting with multiple congenital anomalies, dysmorphic features, and/or intellectual disability. The specific indications for studies include advanced maternal age (>35 yr) or multiple abnormalities on fetal ultrasound (prenatal testing), multiple congenital anomalies, unexplained growth restriction in the fetus or postnatal problems in growth and development, ambiguous genitalia, unexplained intellectual disability with or without associated anatomic abnormalities, primary amenorrhea or infertility, recurrent miscarriages (≥3) or prior history of stillbirths and neonatal deaths, a 1st-degree relative with a known or suspected structural chromosome abnormality, clinical findings consistent with a known anomaly, some malignancies, and chromosome breakage syndromes (e.g., Bloom syndrome, Fanconi anemia).

<table>
<thead>
<tr>
<th>Type of Abnormality</th>
<th>Number</th>
<th>Approximate Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex Chromosome Aneuploidy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males (43,612 newborns)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>47,XXY</td>
<td>45</td>
<td>1/1,000</td>
</tr>
<tr>
<td>47,XY</td>
<td>45</td>
<td>1/1,000</td>
</tr>
<tr>
<td>Other X or Y aneuploidy</td>
<td>32</td>
<td>1/1,350</td>
</tr>
<tr>
<td>Total</td>
<td>122</td>
<td>1/360 male births</td>
</tr>
<tr>
<td>Females (24,547 newborns)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45,X</td>
<td>6</td>
<td>1/4,000</td>
</tr>
<tr>
<td>47,XXX</td>
<td>27</td>
<td>1/900</td>
</tr>
<tr>
<td>Other X aneuploidy</td>
<td>9</td>
<td>1/2,700</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>1/580 female births</td>
</tr>
<tr>
<td><strong>Autosomal Aneuploidy (68,159 Newborns)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>82</td>
<td>1/830</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>9</td>
<td>1/7,500</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>3</td>
<td>1/22,700</td>
</tr>
<tr>
<td>Other aneuploidy</td>
<td>2</td>
<td>1/34,000</td>
</tr>
<tr>
<td>Total</td>
<td>96</td>
<td>1/700 live births</td>
</tr>
<tr>
<td><strong>Structural Abnormalities (68,159 Newborns)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balanced rearrangements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robertsonian</td>
<td>62</td>
<td>1/1,100</td>
</tr>
<tr>
<td>Other</td>
<td>77</td>
<td>1/885</td>
</tr>
<tr>
<td>Unbalanced rearrangements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robertsonian</td>
<td>5</td>
<td>1/13,600</td>
</tr>
<tr>
<td>Other</td>
<td>38</td>
<td>1/1,800</td>
</tr>
<tr>
<td>Total</td>
<td>182</td>
<td>1/375 live births</td>
</tr>
<tr>
<td>All Chromosome Abnormalities</td>
<td>442</td>
<td>1/154 live births</td>
</tr>
</tbody>
</table>

81.1 Methods of Chromosome Analysis
Carlos A. Bacino and Brendan Lee

Cytogenetic studies are usually performed on peripheral blood lymphocytes, although cultured fibroblasts may also be used. Prenatal (fetal) chromosome studies are performed with cells obtained from the amniotic fluid, chorionic villus tissue, and fetal blood or, in the case of preimplantation diagnosis, by analysis of a blastomere. Cytogenetic studies of bone marrow have an important role in tumor surveillance, particularly among patients with leukemia. These are useful to determine induction of remission and success of therapy or, in some cases, the occurrence of relapses.

Chromosome anomalies include abnormalities of number and structure and are the result of errors during cell division. There are 2 types of cell division: mitosis, which occurs in most somatic cells, and meiosis, which is limited to the germ cells. In mitosis, 2 genetically identical daughter cells are produced from a single parent cell. DNA duplication has already occurred during interphase in the S phase of the cell cycle (DNA synthesis). Therefore, at the beginning of mitosis the chromosomes consist of 2 double DNA strands joined together at the centromere known as sister chromatids. Mitosis can be divided into 4 stages: prophase, metaphase, anaphase, and telophase. Prophase is characterized by condensation of the DNA. Also during prophase, the nuclear membrane and the nucleolus disappear and the mitotic spindle forms. In metaphase, the chromosomes are maximally compacted and are clearly visible as distinct structures. The chromosomes align at the center of the cell and spindle fibers connect to the centromere of each chromosome and extend to centrioles at the 2 poles of the mitotic figure. In anaphase, the chromosomes divide along their longitudinal axes to form 2 daughter chromatids, which then migrate to opposite poles of the cell. Telophase is characterized by formation of 2 new nuclear membranes and nucleoli, duplication of the centrioles, and cytoplasmic cleavage to form the 2 daughter cells.

Meiosis begins in the female oocyte during fetal life and is completed years to decades later. In males, it begins in a particular spermatogonial cell sometime between adolescence and adult life and is completed in a few days. Meiosis is preceded by DNA replication so that at the outset each of the 46 chromosomes consists of 2 chromatids. In meiosis, a diploid cell (2n = 46 chromosomes) divides to form haploid cells (n = 23 chromosomes). Meiosis consists of 2 major rounds of cell division. In meiosis I, each of the homologous chromosomes pair precisely so that genetic recombination, involving exchange between 2 DNA strands (crossing over), can occur. This results in a reshuffling of the genetic information on the recombined chromosomes and allows further genetic diversity. Each daughter cell then receives 1 of each of the 23 homologous chromosomes. In meiosis II, the daughter cells receive most of the cytoplasm and becomes the egg, whereas the other smaller cell becomes the first polar body. Meiosis II is similar to a mitotic division but without a preceding round of DNA duplication (replication). Each of the 23 chromosomes divides longitudinally, and the homologous chromatids migrate to opposite poles of the cell. This produces 4 spermatogonia in males, or an egg cell and a second polar body in females, each with a haploid (n = 23) set of chromosomes. Consequently, meiosis fulfills 2 crucial roles: It reduces the chromosome number from diploid (46) to haploid (23) so that upon fertilization a diploid number is restored, and it allows genetic recombination.

Two errors of cell division commonly occur during meiosis or mitosis, and either can result in an abnormal number of chromosomes. The first is nondisjunction, in which 2 chromosomes fail to separate during meiosis and thus migrate together into 1 of the new cells, producing 1 cell with 2 copies of the chromosome and another with no copy. The second is anaphase lag, in which a chromatin or chromosome is lost during mitosis because it fails to move quickly enough during anaphase to become incorporated into 1 of the new daughter cells (Fig. 81-1).

For chromosome analysis, cells are cultured (for varying periods depending on cell type), with or without stimulation, and then artificially arrested in mitosis during metaphase (or prometaphase), later on subjected to a hypotonic solution to allow disruption of the nuclear cell membrane and proper dispersion of the chromosomes for analysis, fixed, banded, and finally stained. The most commonly used banding and staining method is the G-banding (G-bands trypsin Giemsa), also known as G banding, which produces a unique combination of dark (G-positive) and light (G-negative) bands that permits recognition of all individual 23 chromosome pairs for analysis. Other banding techniques, such as Q-banding using quinacrine, reverse banding (R-banding) using acridine orange, and C-banding (constitutive heterochromatin) using barium hydroxide, are available for use in certain circumstances but are losing ground to molecular technologies. Metaphase chromosome spreads are first evaluated microscopically, and then their images are photographed or captured by a video camera and stored on a computer to be later analyzed. Humans have 46 chromosomes or 23 pairs, which are classified as autosomes for chromosomes 1 to 22, and the sex chromosomes, often referred to as sex complement: XX for females and XY for males. The homologous chromosomes from a metaphase spread can then be paired and arranged systematically to assemble a karyotype according to well-defined standard conventions like those established by International
System for Human Cytogenetic Nomenclature (ISCN), with chromosome 1 being the largest and 22 the smallest. According to nomenclature, the description of the karyotype includes the total number of chromosomes followed by the sex chromosome constitution. A normal karyotype is 46,XX for females and 46,XY for males (Fig. 81-2). Abnormalities are noted after the sex chromosome complement.

Although the internationally accepted system for human chromosome classification relies largely on the length and banding pattern of each chromosome, the position of the centromere relative to the ends of the chromosome also is a useful distinguishing feature (Fig. 81-3). The centromere divides the chromosome in 2, with the short arm designated as the **p arm** and the long arm designated as the **q arm**. A plus or minus sign before the number of a chromosome indicates that there is an extra or missing chromosome, respectively. **Table 81-2** lists some of the abbreviations used for the descriptions of chromosomes and their abnormalities. A metaphase chromosome spread usually shows 450-550 bands. Prophase and prometaphase chromosomes are longer, are less condensed, and often show 550-850 bands. High-resolution analysis is useful for detecting subtle chromosome abnormalities that might otherwise go unrecognized.

Molecular techniques such as fluorescence in situ hybridization (FISH) and array comparative genomic hybridization studies (conventional CGH and array CGH [aCGH]) have filled a significant void for diagnosing cryptic chromosomal abnormalities. These techniques identify subtle abnormalities that are often below the resolution of standard cytogenetic studies.

**FISH** is used to identify the presence, absence, or rearrangement of specific DNA segments and is performed with gene- or region-specific DNA probes. Several FISH probes are used in the clinical setting: unique sequence or single-copy probes, repetitive-sequence probes (alpha satellites in the pericentromeric regions), and multiple-copy probes (chromosome specific or painting) (Fig. 81-4A and B). FISH involves using a unique known DNA sequence or probe labeled with a fluorescent dye that is complementary to the studied region of disease interest. The labeled probe is exposed to the DNA on a microscope slide, typically metaphase or interphase chromosomal DNA. When the probe pairs with its complementary DNA sequence, it can then be visualized by fluorescence microscopy (Fig. 81-5). In metaphase chromosome spreads, the exact chromosomal

![Figure 81-3](image-url)  
**Figure 81-3** Example of different chromosome types according to the position of the centromere. On the left is a chromosome pair with the centromere equidistant from the short and long arm (also known as metacentric). In the center is a chromosome 11 pair that is submetacentric. On the right is a chromosome 13 pair that is an example of an acrocentric chromosome. Acrocentric chromosomes contain a very small short arm, stalks, and satellite DNA. The black arrow indicates the position of the centromere. The blue arrow shows the long arm of a chromosome. The red arrow shows the short arm of a chromosome. The green arrow highlights the satellite region, which is made of DNA repeats. The light area between the short arm and the satellite is known as the stalk.

<table>
<thead>
<tr>
<th>ABBREVIATION</th>
<th>MEANING</th>
<th>EXAMPLE</th>
<th>CONDITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>XX</td>
<td>Female</td>
<td>46,XX</td>
<td>Normal female karyotype</td>
</tr>
<tr>
<td>XY</td>
<td>Male</td>
<td>46,XY</td>
<td>Normal male karyotype</td>
</tr>
<tr>
<td>[##]</td>
<td>Number [#] of cells</td>
<td>46,XY[12]/47,XXY[10]</td>
<td>Number of cells in each clone, typically inside brackets Mosaicism in Klinefelter syndrome with 12 normal cells and 10 cells with an extra X chromosome</td>
</tr>
<tr>
<td>cen</td>
<td>Centromere</td>
<td></td>
<td></td>
</tr>
<tr>
<td>del</td>
<td>Deletion</td>
<td>46,XY,del(5p)</td>
<td>Male with deletion of chromosome 5 short arm</td>
</tr>
<tr>
<td>der</td>
<td>Derivative</td>
<td>46,XX,der(2),t(2p127q13)</td>
<td>Female with a structurally rearranged chromosome 2 that resulted from a translocation between chromosomes 2 and 7</td>
</tr>
<tr>
<td>dup</td>
<td>Duplication</td>
<td>46,XY,dup(15)(q11-13)</td>
<td>Male with interstitial duplication in the long arm of chromosome 15 in the Prader-Willi/Angelman syndrome region</td>
</tr>
<tr>
<td>ins</td>
<td>Insertion</td>
<td>46,XY,ins(3)(p13q21q26)</td>
<td>Male with an insertion within chromosome 3 A piece between q21q26 has reinserted on p13</td>
</tr>
<tr>
<td>inv</td>
<td>Inversion</td>
<td>46,XY,inv(2)(p21q31)</td>
<td>Male with pericentric inversion of chromosome 2 with breakpoints at bands p21 and q31</td>
</tr>
<tr>
<td>ABBREVIATION</td>
<td>MEANING</td>
<td>EXAMPLE</td>
<td>CONDITION</td>
</tr>
<tr>
<td>--------------</td>
<td>---------</td>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>ish</td>
<td>Metaphase FISH</td>
<td>46,XX.ish del(7)(q11.23q11.23)</td>
<td>Female with deletion in the Williams syndrome region detected by in situ hybridization</td>
</tr>
<tr>
<td>nuc ish</td>
<td>Interphase FISH</td>
<td>nuc ish(DXZ1 × 3)</td>
<td>Interphase in situ hybridization showing 3 signals for the X chromosome centromeric region</td>
</tr>
<tr>
<td>mar</td>
<td>Marker</td>
<td>47,XY,+mar</td>
<td>Male with extra, unidentified chromosome material</td>
</tr>
<tr>
<td>mos</td>
<td>Mosaic</td>
<td>mos 45,X[14]/46,XX[16]</td>
<td>Turner syndrome mosaicism (analysis of 30 cells showed that 14 cells were 45,X and 16 cells were 46,XX)</td>
</tr>
<tr>
<td>p</td>
<td>Short arm</td>
<td>46,XY,del(5)(p12)</td>
<td>Male with a deletion on the short arm of chromosome 5, band p12 (short nomenclature)</td>
</tr>
<tr>
<td>q</td>
<td>Long arm</td>
<td>46,XY,del(5)(q14)</td>
<td>Male with a deletion on the long arm of chromosome 5, band 14</td>
</tr>
<tr>
<td>r</td>
<td>Ring chromosome</td>
<td>46,X,r(X)(p21q27)</td>
<td>Female with 1 normal X chromosome and a ring X chromosome</td>
</tr>
<tr>
<td>t</td>
<td>Translocation</td>
<td>t(2;8)(q33;q24.1)</td>
<td>The interchange of material between chromosomes 2 and 8 with breakpoints at bands 2q33 and 8q24.1</td>
</tr>
<tr>
<td>ter</td>
<td>Terminal</td>
<td>46,XY,del(5)(p12-pter)</td>
<td>Male with a deletion of chromosome 5 between p12 and the end of the short arm (long nomenclature)</td>
</tr>
<tr>
<td>/</td>
<td>Slash</td>
<td>45,X/46,XY</td>
<td>Separate lines or clones Mosaicism for monosomy X and a male cell line</td>
</tr>
<tr>
<td>+</td>
<td>Gain of</td>
<td>47,XX,+21</td>
<td>Female with trisomy 21</td>
</tr>
<tr>
<td>−</td>
<td>Loss of</td>
<td>45,XY−21</td>
<td>Male with monosomy 21</td>
</tr>
</tbody>
</table>

**Figure 81-4** A, FISH analysis of interphase peripheral blood cells from a patient with Down syndrome using a chromosome 21-specific probe. The 3 red signals mark the presence of 3 chromosomes 21. B, FISH analysis of a metaphase chromosome spread from a clinically normal individual using a whole-chromosome paint specific for chromosome 5. Both chromosomes 5 are completely labeled (yellow) along their entire length. C, FISH on metaphase cells using a unique sequence probe that hybridizes to the elastin gene on chromosome 7q11.23, inside the Williams syndrome critical region. The elastin probe is labeled in red, and a control probe on chromosome 7 is labeled in green. The left image shows normal hybridization to chromosome 7, with 2 signals for the elastin region and 2 for the control probe. The right image shows a normal chromosome on the right with control and elastin signals, and a deleted chromosome 7 on the left, evidenced by a single signal for the control probe. This image corresponds to a patient with a Williams syndrome region deletion.
Figure 81-5 FISH involves denaturation of double-stranded DNA as present in metaphase chromosomes or interphase nuclei on cytogenetic slide preparations (A) into single-stranded DNA (B). The slide-bound (in situ) DNA is then renatured or reannealed in the presence of excess copies of a single-stranded, fluorochrome-labeled DNA base-pair sequence or probe (C). The probe anneals or “hybridizes” to sites of complementary DNA sequence (D) within the chromosomal genome. Probe signal is visualized and imaged on the chromosome by fluorescent microscopy. (From Lin RL, Cherry AM, Bangs CD, et al: FISHing for answers: the use of molecular cytogenetic techniques in adolescent medicine practice. In Hyme HE, Greydanus D, editors: Genetic disorders in adolescents: state of the art reviews. Adolescent medicine, Philadelphia, 2002, Hanley and Belfus, pp. 305–313.)

Figure 81-4, cont’d D, FISH in interphase cells using DNA probes that hybridize to repetitive α-satellite sequences in the pericentromeric region for the sex chromosomes. Left, interphase cells with 2 signals, 1 labeled in red for the X chromosome and green for the Y chromosome, consistent with a normal male chromosome complement. Right, interphase cell showing 2 red signals for the X chromosome, compatible with a normal female chromosome complement.
location of each probe copy can be documented and often the number of copies (deletions, duplications) of the DNA sequence as well. When the interrogated segments (as in genomic duplications) are close together, only interphase cells can accurately determine the presence of 2 or more copies or signals since in metaphase cells, some duplications might falsely appear as a single signal.

With high-resolution chromosome analysis it is very difficult to recognize deletions of <5 million bp (5 Mbp); FISH can reliably detect deletions as small as 50-200 kb of DNA. This has allowed the clinical characterization of a number of microdeletion syndromes. Other probes hybridize to repetitive sequences located to the pericentromeric regions. Pericentromeric probes are still widely used for the rapid identification of certain trisomies in interphase cells of blood smears, or even in the rapid analysis of prenatal samples from cells obtained through amniocentesis. Such probes are available for chromosomes 13, 18, and 21 and for the sex pair X and Y (see Fig. 81-4C and D). With regards to the detection of genomic disorders, FISH is no longer the first line of testing, and its role has also mostly changed to the confirmation of microarray findings.

Spectral karyotyping and multicolor FISH are similar molecular cytogenetic techniques that use 24 different chromosome painting probes and 5 fluorochromes to simultaneously visualize every chromosome. CGH is a molecular-based technique that involves differentially labeling the patient's DNA with a fluorescent dye (green) and a normal reference DNA with another fluorescent dye (red; Fig. 81-6). Equal amounts of the 2-label DNA samples are mixed and then used as a painting probe for FISH with normal metaphase chromosomes. The ratio of green:red fluorescence is measured along each chromosome. Regions of amplification of the patient's DNA display an excess of green fluorescence, and regions of loss show excess red fluorescence. If the patient's and the control DNA are equally represented, the green:red ratio is 1:1 and the chromosomes appear yellow.

A modified version of this technology, aCGH, uses DNA spotted onto a slide or microarray grid. In this case, instead of metaphase

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**Figure 81-6** An example of a cryptic microdeletion at a translocation breakpoint of an apparently balanced translocation in a patient with DD and growth defect. A, Partial karyotype shows t(15;22)(q26.1;q11.2). B, FISH with clones 2O19 (green) and 354M14 (red) at 15q26.1; arrows indicate signals only present on the normal chromosome 15, suggesting a deletion on the der(15). C, Two-color aCGH with dye swap with 244 K oligo probes; arrowhead indicates a 3.3-Mbp deletion at chromosome 15q26.1-q26.2, arrow points to the close-up view of the deletion. (From Li MM, Andersson HC: Clinical application of microarray-based molecular cytogenetics: an emerging new era of genomic medicine, J Pediatr 155:311-317, 2009, with permission of the authors and publisher.)
chromosomes, segments of DNA are represented by oligonucleotides (short DNA segments) distributed in a microarray that resembles the chromosomes in a metaphase. The detection is currently possible at the single exon resolution level depending on the arrays employed. There are many advantages of aCGH. It can test all critical disease-causing regions in the genome at once; FISH requires the clinical knowledge and tests only 1 area at a time. aCGH can detect duplications and deletions not currently recognized as recurrent disease-causing regions probed by FISH. aCGH can detect single and contiguous gene deletion syndromes. aCGH does not always require cell culture to generate sufficient DNA, something that may be important in the context of prenatal testing because of timing. There are disadvantages to aCGH: It does not detect balanced translocations, inversions, or very low-levels of mosaicism.

There are different types of aCGH; some of them are more targeted while others have whole-genome coverage. Targeted aCGH is an effective and efficient technique for detecting clinically known cryptic chromosomal aberrations, which are typically associated with known disease phenotypes; many of these arrays have expanded detection to areas potentially susceptible to recurring deletion or duplication.

Whole-genome arrays target the entire genome. The advantage of this latter technique is that it allows better and denser coverage of the entire genome in evenly spaced portions; its disadvantage is that interpretation of deletions or duplications may be difficult if it involves areas not previously known to be involved in disease. There is a new type of array being used in the clinical setting and that is the so-called single nucleotide polymorphism (SNP) array. SNPs are polymorphic variations between 2 nucleotides and when analyzed in massive parallel fashion, they can provide very valuable clinical information. Several million SNPs normally occur in the human genome. SNP arrays can help with the detection of uniparental disomies as well as consanguinity. Many arrays currently used in clinical practice combine the use of oligonucleotides for the detection of copy number variations in conjunction with SNPs.

There are many copy number variations causing deletion or duplication in the human genome. Thus, most detected genetic abnormalities, unless associated with very well-known clinical phenotypes, require parental investigations because a detected copy number variation that is inherited might turn out to be an incidental polymorphic variant. A de novo abnormality (i.e., one found only in the child and not the parents) is often more significant if it is associated with an abnormal phenotype found only in the child and if it involves genes with important functions. aCGH is a very valuable technology alone or when combined with FISH and conventional chromosome studies (Fig. 81-7).

Bibliography is available at Expert Consult.

81.2 Down Syndrome and Other Abnormalities of Chromosome Number
Brendan Lee

ANEUPLOIDY AND POLYPLOIDY
Human cells contain a multiple of 23 chromosomes (n = 23). A haploid cell (n) has 23 chromosomes (typically in the ovum or sperm). If a cell’s chromosomes are an exact multiple of 23 (46, 69, 92 in humans), those cells are referred to as euploid. Polyploid cells are euploid cells with more than the normal diploid number of 46 (2n) chromosomes: 3n, 4n. Polyploid conceptions are usually not viable, but the presence of mosaicism with a karyotypically normal line can allow survival. Mosaicism is an abnormality defined as the presence of 2 or more cell lines in a single individual. Polyploidy is a common abnormality seen in 1st-trimester pregnancy losses. Trioid cells are those with 3 haploid sets of chromosomes (3n) and are only viable in a mosaic form. Triploid infants can be liveborn but do not survive long. Triploidy is often the result of fertilization of an egg by 2 sperm (dispermy). Failure of 1 of the meiotic divisions, resulting in a diploid egg or sperm, can also result in triploidy. The phenotype of a triploid conception depends on the origin of the extra chromosome set. If the extra set is of maternal origin, it results in a partial hydatidiform mole with poor embryonic development, but triploid conceptions that have an extra set of maternal chromosomes results in severe embryonic retardation with a small fibrotic placenta that is typically spontaneously aborted.

Abnormal cells that do not contain a multiple of haploid number of chromosomes are termed aneuploid cells. Aneuploidy is the most common and clinically significant type of human chromosome abnormality, occurring in at least 3–4% of all clinically recognized pregnancies. Monosomies occur when only 1, instead of the normal 2, of a given chromosome is present in an otherwise diploid cell. In humans,
Bibliography

Petherick A: Cell-free DNA screening for trisomy is rolled out in Israel, Lancet 382:846, 2013.
most autosomal monosomies appear to be lethal early in development, and survival is possible in mosaic forms or by means of chromosome rescue (restoration of the normal number by duplication of single monosomic chromosome). An exception to this rule is monosomy for the X chromosome (45,X), seen in Turner syndrome; it has been estimated that the majority of 45,X conceptuses are lost early in pregnancy for as yet unexplained reasons.

The most common cause of aneuploidy is nondisjunction, the failure of chromosomes to disjoin normally during meiosis (see Fig. 81-1). Nondisjunction can occur during meiosis I or II or during mitosis. After meiotic nondisjunction, the resulting gamete either lacks a chromosome or has 2 copies instead of 1 normal copy, resulting in a monosomic or trisomic zygote, respectively.

Trisomy is characterized by the presence of 3 chromosomes, instead of the normal 2, of any particular chromosome. Trisomy is the most common form of aneuploidy. Trisomy can occur in all cells or it may be mosaic. Most individuals with trisomy exhibit a consistent and specific phenotype depending on the chromosome involved.

FISH is a technique that can be used for rapid diagnosis in the prenatal detection of common fetal aneuploidies including chromosomes 13, 18, and 21, as well as sex chromosomes (see Fig. 81-4C and D).

The most common numerical abnormalities in liveborn children include trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome), trisomy 13 (Patau syndrome), and sex chromosomal aneuploidies: Turner syndrome (usually 45,X), Klinefelter syndrome (47,XXY), 47,XXX, and 47,XY,Y. By far the most common type of trisomy in liveborn infants is trisomy 21 (47,XX,+21 or 47,XY,+21) (see Table 81-1). Trisomy 18 and trisomy 13 are relatively less common and are associated with a characteristic set of congenital anomalies and severe intellectual disability (Table 81-3). The occurrence of trisomy 21 and other trisomies increases with advanced maternal age (≥35 yr). Owing to this increased risk, women who are ≥35 yr at the time of delivery should be offered genetic counseling and prenatal diagnosis (including serum screening, ultrasonography, and amniocentesis or chorionic villus sampling; see Chapter 96).

### DOWN SYNDROME

Trisomy 21 is the most common genetic cause of moderate intellectual disability. The incidence of Down syndrome in live births is approximately 1 in 733; the incidence at conception is more than twice that rate; the difference is accounted by early pregnancy losses. In addition to cognitive impairment, Down syndrome is associated with congenital anomalies and characteristic dysmorphic features (Figs. 81-8 and 81-9; Table 81-4). Although there is variability in the clinical features, the constellation of phenotypic features is fairly consistent and permits clinical recognition of trisomy 21. Affected individuals are more prone to congenital heart defects (50%) such as atrioventricular septal defects, ventricular septal defects, isolated secundum atrial septal defects,

### Table 81-3 | Chromosomal Trisomies and Their Clinical Findings

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>CLINICAL MANIFESTATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 13, Patau syndrome</td>
<td>1/10,000 births</td>
</tr>
<tr>
<td></td>
<td>Early lethality in most cases, with a median survival of 7 days; ~91% die by 1 year. Survivors have significant neurodevelopmental delay</td>
</tr>
<tr>
<td>Trisomy 18, Edwards syndrome</td>
<td>1/6,000 births</td>
</tr>
<tr>
<td></td>
<td>~92% of children die in the first year, with full support ~25% may survive 1 yr. Survivors have significant neurodevelopmental delay</td>
</tr>
<tr>
<td>Trisomy 8, mosaicism</td>
<td>1/20,000 births</td>
</tr>
</tbody>
</table>

*Figure 81-8* A, Face of a child with Down syndrome. B, Karyotype of a male with trisomy 21 as seen in Down syndrome. This karytype reveals 47 chromosomes instead of 46, with an extra chromosome in pair 21.
patent ductus arteriosus, and tetralogy of Fallot. Congenital and acquired gastrointestinal anomalies and hypothyroidism are common (Table 81-5). Other abnormalities include megakaryoblastic leukemia, immune dysfunction, diabetes mellitus, and problems with hearing and vision (Table 81-5). Alzheimer disease–like dementia is a known complication that occurs as early as the 4th decade and has an incidence 2-3 times higher than sporadic Alzheimer disease. Most males with Down syndrome are sterile, but some females have been able to reproduce, with a 50% chance of having trisomy 21 pregnancies. Two genes (DYRK1A, DSCR1) in the putative critical region of chromosome 21 may be targets for therapy.

Developmental delay is universal (Tables 81-6 and 81-7; Fig. 81-10). Cognitive impairment does not uniformly affect all areas of development. Social development is relatively spared, but children with Down syndrome have considerable difficulty using expressive language. Understanding these individual developmental strengths will maximize the educational process for children with Down syndrome. Persons with Down syndrome often benefit from programs aimed at stimulation, development, and education. These programs are most effective in addressing social skills that often appear advanced for the intellectual delay. Children with Down syndrome also benefit from anticipatory guidance, which establishes the protocol for screening, evaluation, and care for patients with genetic syndromes and chronic disorders (Table 81-8). Up to 15% of children with Down syndrome have misalignment of cervical vertebra C1, which places them at risk for spinal cord injury with neck hyperextension or extreme flexion. Special Olympics recommends sports participation and training but requires x-ray examination (full extension and flexion views) of the neck prior to participation in sports that may result in hyperextension or radical flexion or pressure on the neck or upper spine; sports include diving starts in swimming, butterfly stroke, diving, pentathlon, high jump, equestrian sports, gymnastics, football, soccer, alpine skiing, and warm up exercises placing stress on the head and neck. If atlantoaxial instability is diagnosed, Special Olympics will permit participation if the parents or guardians request so and only after obtaining written certification from a physician and acknowledgment of the risks by the parent or guardian.

The majority of children with Down syndrome do not have behavior problems. It is estimated that psychiatric comorbidity is 18-38% in this population. These estimates are higher than in unaffected children, but they are lower than in children with similar levels of intellectual disability from other etiologies. All maladaptive behaviors in persons with Down syndrome are stereotype, but they are lower than in children with similar levels of intellectual delay. The life expectancy for children with Down syndrome is reduced and is approximately 50-55 yr. Little prospective information about the secondary medical problems of adults with Down syndrome is known. Retrospective studies have shown premature aging and an increased risk of Alzheimer disease in adults with Down syndrome. These studies have also shown unexpected negative associations between Down syndrome and other medical comorbidities. Persons with Down syndrome have fewer than expected deaths caused by solid tumors and ischemic heart disease. This same study reported increased risk of adult deaths due to congenital heart disease, seizures, and leukemia. In one large study, leukemias accounted for 60% of all cancers in people with Down syndrome.

### Table 81-4 Clinical Features of Down Syndrome in the Neonatal Period

<table>
<thead>
<tr>
<th>CENTRAL NERVOUS SYSTEM</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotonia*</td>
<td></td>
</tr>
<tr>
<td>Developmental delay</td>
<td></td>
</tr>
<tr>
<td>Poor Moro reflex*</td>
<td></td>
</tr>
<tr>
<td>CRANIOFACIAL</td>
<td></td>
</tr>
<tr>
<td>Brachycephaly with flat occiput</td>
<td></td>
</tr>
<tr>
<td>Flat face*</td>
<td></td>
</tr>
<tr>
<td>Upward slanted palpebral fissures*</td>
<td></td>
</tr>
<tr>
<td>Epicanthal folds</td>
<td></td>
</tr>
<tr>
<td>Speckled irises (Brushfield spots)</td>
<td></td>
</tr>
<tr>
<td>Three fontanels</td>
<td></td>
</tr>
<tr>
<td>Delayed fontanel closure</td>
<td></td>
</tr>
<tr>
<td>Frontal sinus and midfacial hypoplasia</td>
<td></td>
</tr>
<tr>
<td>Mild microcephaly</td>
<td></td>
</tr>
<tr>
<td>Short hard palate</td>
<td></td>
</tr>
<tr>
<td>Small nose, flat nasal bridge</td>
<td></td>
</tr>
<tr>
<td>Protruding tongue, open mouth</td>
<td></td>
</tr>
<tr>
<td>Small dysplastic ears*</td>
<td></td>
</tr>
<tr>
<td>CARDIOVASCULAR</td>
<td></td>
</tr>
<tr>
<td>Endocardial Cushing defects</td>
<td></td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td></td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td></td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td></td>
</tr>
<tr>
<td>Aberrant subclavian artery</td>
<td></td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td></td>
</tr>
<tr>
<td>MUSCULOSKELETAL</td>
<td></td>
</tr>
<tr>
<td>Joint hyper flexibility*</td>
<td></td>
</tr>
<tr>
<td>Short neck, redundant skin*</td>
<td></td>
</tr>
<tr>
<td>Short metacarpals and phalanges</td>
<td></td>
</tr>
<tr>
<td>Short 5th digit with clinodactyly*</td>
<td></td>
</tr>
<tr>
<td>Single transverse palmar creases*</td>
<td></td>
</tr>
<tr>
<td>Wide gap between 1st and 2nd toes</td>
<td></td>
</tr>
<tr>
<td>Pelvic dysplasia*</td>
<td></td>
</tr>
<tr>
<td>Short sternum</td>
<td></td>
</tr>
<tr>
<td>Two sternal manubrium ossification centers</td>
<td></td>
</tr>
<tr>
<td>GASTROINTESTINAL</td>
<td></td>
</tr>
<tr>
<td>Duodenal atresia</td>
<td></td>
</tr>
<tr>
<td>Annular pancreas</td>
<td></td>
</tr>
<tr>
<td>Tracheoesophageal fistula</td>
<td></td>
</tr>
<tr>
<td>Hirschprung disease</td>
<td></td>
</tr>
<tr>
<td>Imperforate anus</td>
<td></td>
</tr>
<tr>
<td>Neonatal cholestasis</td>
<td></td>
</tr>
<tr>
<td>CUTANEOUS</td>
<td></td>
</tr>
<tr>
<td>Cuts marmorata</td>
<td></td>
</tr>
</tbody>
</table>

*Hall’s criteria to aid in diagnosis.
syndrome and 97% of all cancers in children with Down syndrome. There was decreased risk of solid tumors in all age groups, including neuroblastomas and nephroblastomas in children with Down syndrome and epithelial tumors in adults with Down syndrome.

Most adults with Down syndrome are able to perform activities of daily living. However, most adults with Down syndrome have difficulty with complex financial, legal, or medical decisions. In most circumstances, a conservator is appointed for the adult with Down syndrome.

The risk of having a child with trisomy 21 is highest in women who conceive at >35 yr of age. Even though younger women have a lower risk, they represent half of all mothers with babies with Down syndrome because of their higher overall birth rate.

All women should be offered screening for Down syndrome in their 2nd trimester by means of 4 maternal serum tests (free β-human chorionic gonadotropin [β-hCG], unconjugated estriol, inhibin, and α-fetoprotein). This is
known as the quad screen; it can detect up to 80% of Down syndrome pregnancies compared to 70% in the triple screen. Both tests have a 5% false-positive rate. There is a method of screening during the 1st trimester using fetal nuchal translucency (NT) thickness that can be done alone or in conjunction with maternal serum β-hCG and pregnancy-associated plasma protein-A (PAPP-A). In the 1st trimester, NT alone can detect ≤70% of Down syndrome pregnancies, but with β-hCG and PAPP-A, the detection goes up to 87%. If both 1st and 2nd trimester screens are combined using NT and biochemical profiles (integrated screen), the detection rate goes up to 95%. If only 1st trimester quad screening is done, maternal serum α-fetoprotein (which is decreased in affected pregnancies) is recommended as a 2nd trimester follow-up.

Detection of cell free fetal DNA in maternal plasma is also diagnostic. The noninvasive detection of fetal trisomy 21 by analyzing cell-free fetal DNA in maternal serum is an important advance in prenatal diagnosis of Down syndrome. Next-generation DNA sequencing has reduced the cost of this procedure, which has a high degree of accuracy (98% detection rate) and applicability. The prenatal screens are also useful for other trisomies, although the detection rates may be different from those given for Down syndrome.

In approximately 95% of the cases of Down syndrome there are 3 copies of chromosome 21. The majority of translocations in Down syndrome are fusions at the centromere between chromosomes 13, 14, 15, 21, and 22 known as Robertsonian translocations. The translocations can be de novo or inherited. Very rarely is Down syndrome diagnosed in a patient with only a part of the long arm of chromosome 21 in triplicate (partial trisomy). Isochromosomes and ring chromosomes are other rarer causes of trisomy 21. Down syndrome patients without a visible chromosome abnormality are the least common. It is not possible to distinguish the phenotypes of persons with full trisomy 21 and those with a translocation. Representative genes on chromosome 21 and their potential effects on development are noted in Table 81-9. Patients who are mosaic tend to have a milder phenotype.

Chromosome analysis is indicated in every person suspected of having Down syndrome. If a translocation is identified, parental chromosome studies must be performed to determine whether one of the parents is a translocation carrier, which carries a high recurrence risk for having another affected child. That parent might also have other family members at risk. Translocation (21;21) carriers have a 100% recurrence risk for a chromosomally abnormal child, and other Robertsonian translocations, such as t(14;21), have a 5-7% recurrence risk when transmitted by females. Genomic dosage imbalance contributes through direct and indirect pathways to the Down syndrome phenotype and its phenotypic variation.

Tables 81-10 and 81-11 provide more information on other aneuploidies and partial autosomal aneuploidies (Figs. 81-11 to 81-14).

Bibliography is available at Expert Consult.
**Table 81-9** Genes Localized to Chromosome 21 That Possibly Affect Brain Development, Neuronal Loss, and Alzheimer Type Neuropathology

<table>
<thead>
<tr>
<th>SYMBOL</th>
<th>NAME</th>
<th>POSSIBLE EFFECT IN DOWN SYNDROME</th>
<th>FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIM2</td>
<td>Single-minded homolog 2</td>
<td>Brain development</td>
<td>Required for synchronized cell division and establishment of proper cell lineage</td>
</tr>
<tr>
<td>DYRK1A</td>
<td>Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A</td>
<td>Brain development</td>
<td>Expressed during neuroblast proliferation Believed important homolog in regulating cell-cycle kinetics during cell division</td>
</tr>
<tr>
<td>GART</td>
<td>Phosphoribosylglycinamide formyltransferase</td>
<td>Brain development</td>
<td>Expressed during prenatal development of the cerebellum</td>
</tr>
<tr>
<td>PCP4</td>
<td>Purkinje cell protein 4</td>
<td>Brain development</td>
<td>Function unknown but found exclusively in the brain and most abundantly in the cerebellum</td>
</tr>
<tr>
<td>DSCAM</td>
<td>Down syndrome cell adhesion molecule</td>
<td>Brain development and possible candidate gene for congenital heart disease</td>
<td>Expressed in all molecule regions of the brain and believed to have a role in axonal outgrowth during development of the nervous system</td>
</tr>
<tr>
<td>GRIK1</td>
<td>Glutamate receptor, ionotropic kainite1</td>
<td>Neuronal loss</td>
<td>Function unknown, found in the cortex in fetal and early postnatal life and in adult primates, most concentrated in pyramidal cells in the cortex</td>
</tr>
<tr>
<td>APP</td>
<td>Amyloid beta (A4) precursor protein (protease nexin-II, Alzheimer disease)</td>
<td>Alzheimer type neuropathy</td>
<td>Seems to be involved in plasticity, neurite outgrowth, and neuroprotection</td>
</tr>
<tr>
<td>S100B</td>
<td>S100 calcium binding protein β (neural)</td>
<td>Alzheimer type neuropathy</td>
<td>Stimulates glial formation</td>
</tr>
<tr>
<td>SOD1</td>
<td>Superoxide dismutase 1, soluble (amyotrophic lateral sclerosis, adult)</td>
<td>Accelerated aging?</td>
<td>Scavenges free superoxide molecules in the cell and might accelerate aging by producing hydrogen peroxide and oxygen</td>
</tr>
</tbody>
</table>

**Table 81-10** Other Rare Aneuploidies and Partial Autosomal Aneuploidies

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>KARYOTYPE</th>
<th>CLINICAL MANIFESTATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 8</td>
<td>47,XX/XY,+8</td>
<td>Growth and mental deficiency are variable The majority of patients are mosaics Deep palmar and plantar furrows are characteristic</td>
</tr>
<tr>
<td>Trisomy 9</td>
<td>47,XX/XY,+9</td>
<td>The majority of patients are mosaics Clinical features include craniofacial (high forehead, microphthalmia, low-set malformed ears, bulbous nose) and skeletal (joint contractures) malformations and heart defects (60%)</td>
</tr>
<tr>
<td>Trisomy 16</td>
<td>47,XX/XY,+16</td>
<td>The most commonly observed autosomal aneuploidy in spontaneous abortion; the recurrence risk is negligible</td>
</tr>
<tr>
<td>Tetrasomy 12p</td>
<td>46,XX[12]/46,XX, +i(12p)[8] (mosaicism for an isochromosome 12p)</td>
<td>Known as Pallister-Killian syndrome. Sparse anterior scalp hair, eyebrows, and eyelashes, prominent forehead, chubby cheeks, long philtrum with thin upper lip and cupid-bow configuration, polydactyly, and streaks of hyper- and hypopigmentation</td>
</tr>
</tbody>
</table>

**Table 81-11** Findings That May Be Present in Trisomy 13 and Trisomy 18

<table>
<thead>
<tr>
<th>TRISOMY 13</th>
<th>TRISOMY 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEAD AND FACE</td>
<td></td>
</tr>
<tr>
<td>Scalp defects (e.g., cutis aplasia)</td>
<td>Small and premature appearance</td>
</tr>
<tr>
<td>Microphthalmia, corneal abnormalities</td>
<td>Tight palpebral fissures</td>
</tr>
<tr>
<td>Cleft lip and palate in 60%-80% of cases</td>
<td>Narrow nose and hypoplastic nasal alae</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>Narrow bifrontal diameter</td>
</tr>
<tr>
<td>Microphthalmia</td>
<td>Prominent occiput</td>
</tr>
<tr>
<td>Sloping forehead</td>
<td>Micrognathia</td>
</tr>
<tr>
<td>Holoprosencephaly (arhinencephaly)</td>
<td>Cleft lip or palate</td>
</tr>
<tr>
<td>Capillary hemangiomas</td>
<td>Microcephaly</td>
</tr>
<tr>
<td>Deafness</td>
<td></td>
</tr>
<tr>
<td>CHEST</td>
<td></td>
</tr>
<tr>
<td>Congenital heart disease (e.g., VSD, PDA, and ASD) in 80% of cases</td>
<td>Congenital heart disease (e.g., VSD, PDA, ASD)</td>
</tr>
<tr>
<td>Thin posterior ribs (missing ribs)</td>
<td>Short sternum, small nipples</td>
</tr>
</tbody>
</table>
Table 81-11  Findings That May Be Present in Trisomy 13 and Trisomy 18—cont’d

<table>
<thead>
<tr>
<th>TRISOMY 13</th>
<th>TRISOMY 18</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EXTREMITIES</strong></td>
<td></td>
</tr>
<tr>
<td>Overlapping of fingers and toes (clinodactyly)</td>
<td>Limited hip abduction</td>
</tr>
<tr>
<td>Polydactyly</td>
<td>Clinodactyly and overlapping fingers; index over 3rd, 5th over 4th; closed fist</td>
</tr>
<tr>
<td>Hypoplastic nails, hyperconvex nails</td>
<td>Rocker-bottom feet</td>
</tr>
<tr>
<td></td>
<td>Hypoplastic nails</td>
</tr>
<tr>
<td><strong>GENERAL</strong></td>
<td></td>
</tr>
<tr>
<td>Severe developmental delays and prenatal and postnatal growth restriction</td>
<td>Severe developmental delays and prenatal and postnatal growth restriction</td>
</tr>
<tr>
<td>Renal abnormalities</td>
<td>Premature birth, polyhydramnios</td>
</tr>
<tr>
<td>Only 5% live &gt;6 mo</td>
<td>Inguinal or abdominal hernias</td>
</tr>
<tr>
<td></td>
<td>Only 5% live &gt;1 yr</td>
</tr>
</tbody>
</table>

ASD, atrial septal defect; PDA, patent ductus arteriosus; VSD, ventricular septal defect.


**Figure 81-11** Facial appearance of a child with trisomy 13. (From Wiedemann HR, Kunze J, Dibbern H: Atlas of clinical syndromes: a visual guide to diagnosis, ed 3, St. Louis, 1989, Mosby.)

**Figure 81-12** Trisomy 18: overlapping fingers and hypoplastic nails. (From Wiedemann HR, Kunze J, Dibbern H: Atlas of clinical syndromes: a visual guide to diagnosis, ed 3, St. Louis, 1989, Mosby.)

**Figure 81-13** Trisomy 18: rocker-bottom feet (protruding calcanei). (From Wiedemann HR, Kunze J, Dibbern H: Atlas of clinical syndromes: a visual guide to diagnosis, ed 3, St. Louis, 1989, Mosby.)

**Figure 81-14** Male infant with trisomy 18 at age 4 days. Note prominent occiput, micrognathia, low-set ears, short sternum, narrow pelvis, prominent calcaneus, and flexion abnormalities of the fingers.
Bibliography

81.3 Abnormalities of Chromosome Structure

Carlos A. Bacino and Brendan Lee

TRANSLOCATIONS

Translocations, which involve the transfer of material from 1 chromosome to another, occur with a frequency of 1 in 500 liveborn human infants. They may be inherited from a carrier parent or appear de novo, with no other affected family member. Translocations are commonly reciprocal or Robertsonian, involving 2 chromosomes (Fig. 81-15).

Reciprocal translocations are the result of breaks in nonhomologous chromosomes, with reciprocal exchange of the broken segments. Carriers of a reciprocal translocation are usually phenotypically normal but are at an increased risk for miscarriage caused by transmission of unbalanced reciprocal translocations and for bearing chromosomally abnormal offspring. Unbalanced translocations are the result of abnormalities in the segregation or crossover of the translocation carrier chromosomes in the germ cells.

Robertsonian translocations involve 2 acrocentric chromosomes (chromosomes 13, 14, 21, and 22) that fuse near the centromeric region with a subsequent loss of the short arms. Because the short arms of all 5 pairs of acrocentric chromosomes have multiple copies of genes for ribosomal RNA, loss of the short arm of 2 acrocentric chromosomes has no deleterious effect. The resulting karyotype has only 45 chromosomes, including the translocated chromosome that is made up of the long arms of the 2 fused chromosomes. Carriers of Robertsonian translocations are usually phenotypically normal.

However, they are at increased risk for miscarriage and unbalanced translocations in phenotypically abnormal offspring.

In some rare instances, translocations can involve 3 or more chromosomes, as seen in complex rearrangements. Another, less common type is the insertional translocation. Insertional translocations result from a piece of chromosome material that breaks away and later is reinserted inside the same chromosome at a different site or inserted in another chromosome.

INVERSIONS

An inversion requires that a single chromosome break at 2 points; the broken piece is then inverted and joined into the same chromosome. Inversions occur in 1 in 100 live births. There are 2 types of inversions: pericentric and paracentric. In pericentric inversions, the breaks are in the 2 opposite arms of the chromosome and include the centromere. They are usually discovered because they change the position of the centromere. The breaks in paracentric inversions occur in only 1 arm. Carriers of inversions are usually phenotypically normal, but they are at increased risk for miscarriages, typically in paracentric inversions, and chromosomally abnormal offspring in pericentric inversions.

DELETIONS AND DUPLICATIONS

Deletions involve loss of chromosome material and, depending on their location, they can be classified as terminal (at the ends of chromosomes) or interstitial (within the arms of a chromosome). They may be isolated or they may occur along with a duplication of another chromosome segment. The latter typically occurs in unbalanced reciprocal chromosomal translocation secondary to abnormal crossover or segregation in a translocation or inversion carrier.

A carrier of a deletion is monosomic for the genetic information of the missing segment. Deletions are usually associated with intellectual disability and malformations. The most commonly observed deletions in routine chromosome preparations include 1p−, 4p−, 5p−, 9p−, 11p−, 13q−, 18p−, 18q−, and 21q− (Table 81-12 and Fig. 81-16), all distal or terminal deletions of the short or the long arms of chromosomes. Deletions may be observed in routine chromosome preparations, and deletions and translocations larger than 5-10 Mbp are usually visible microscopically.

High-resolution banding techniques, FISH, and molecular studies like aCGH can reveal deletions that are too small to be seen in ordinary or routine chromosome spreads (see Fig. 81-7). Microdeletions involve loss of small chromosome regions, the largest of which are detectable only with prophase chromosome studies and/or molecular methods. For submicroscopic deletions, the missing piece can only be detected using molecular methodologies such as DNA-based studies like aCGH or FISH. The presence of extra genetic material from the same chromosome is referred to as duplication. Duplications can also be sporadic or result from abnormal segregation in translocation or inversion carriers.

Microdeletions and microduplications usually involve regions that include several genes, so that the affected individuals can have a distinctive phenotype depending on the number of genes involved. When such a deletion involves more than a single gene, the condition is referred to as a contiguous gene deletion syndrome (Table 81-13). With the advent of clinically available aCGH, a large number of duplications, most of them microduplications, have been uncovered. Most of those microduplication syndromes are the reciprocal duplications of the known deletions or microdeletion counterparts and have distinctive clinical features (Table 81-14).

Subtelomeric regions are often involved in chromosome rearrangements that cannot be visualized using routine cytogenetics. Telomeres, which are the distal ends of the chromosomes, are gene-rich regions. The distal structure of the telomeres is essentially common to all chromosomes, but proximal to those, there are unique regions known as subtelomeres, which typically involved in deletions and most other chromosome rearrangements. Small subtelomeric deletions, duplications, or rearrangements (translocations, inversions) may be relatively common in nonspecific intellectual disability with minor anomalies. Subtelomeric rearrangements have been found in 3-7% of children.

Figure 81-15 A, Schematic diagram (left) and partial G-banded karyotype (right) of a reciprocal translocation between chromosome 2 (blue) and chromosome 8 (pink). The breakpoints are on the long (q) arm of both chromosomes at bands 2q33 and 8q24.1, with the reciprocal exchange of material between the derivative (der) chromosomes 2 and 8. This translocation is balanced, with no net gain or loss of material. The nomenclature for this exchange is t(2;8)(q33;q24.1). B, Schematic diagram (left) and partial G-banded karyotype (right) of a Robertsonian translocation between chromosomes 13 (blue) and 14 (pink). The breakpoints are at the centromere (band q10) of both chromosomes, with fusion of the long arms into a single derivative chromosome and loss of the short (p) arm material. The nomenclature for this exchange is der(13;14)(q10;q10).
### Table 81-12  
Common Deletions and Their Clinical Manifestations

<table>
<thead>
<tr>
<th>DELETION</th>
<th>CLINICAL ABNORMALITIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>4p−</td>
<td>Wolf-Hirschhorn syndrome. The main features are a typical &quot;Greek helmet&quot; facies secondary to ocular hypertelorism, prominent glabella, and frontal bossing; microcephaly, dolichocephaly, hypoplasia of the orbits, ptosis, strabismus, nystagmus, bilateral epicanthic folds, cleft lip and palate, beaked nose with prominent bridge, hypospadias, cardiac malformations, and intellectual disability.</td>
</tr>
<tr>
<td>5p−</td>
<td>Cri-du-chat syndrome. The main features are hypotonia, short stature, characteristic shrill cry in the first few weeks of life (cat-like cry), microcephaly with protruding metopic suture, hypertelorism, bilateral epicanthic folds, high arched palate, wide and flat nasal bridge, and intellectual disability.</td>
</tr>
<tr>
<td>9p−</td>
<td>The main features are craniofacial dysmorphology with trigonocephaly, slanted palpebral fissures, discrete exophthalmos secondary to supraorbital hypoplasia, arched eyebrows, flat and wide nasal bridge, short neck with low hairline, genital anomalies, long fingers and toes with extra flexion creases, cardiac malformations, and intellectual disability.</td>
</tr>
<tr>
<td>13q−</td>
<td>The main features are low birthweight, failure to thrive, microcephaly, and severe intellectual disability. Facial features include high wide nasal bridge, hypertelorism, ptosis, micrognathia. Ocular malformations are common (retinoblastoma). The hands have hypoplastic or absent thumbs and syndactyly.</td>
</tr>
<tr>
<td>18p−</td>
<td>A few patients (15%) are severely affected and have cephalic and ocular malformations: holoprosencephaly, cleft lip and palate, ptosis, epicanthal folds, and varying degrees of intellectual disability. Most (80%) have only minor malformations and mild intellectual disability.</td>
</tr>
<tr>
<td>18q−</td>
<td>Growth deficiency, hypotonia with “frog-like” position with the legs flexed, externally rotated, and in hyperabduction. The face is characteristic with depressed midface and apparent protrusion of the mandible, deep-set eyes, short upper lip, everted lower lip (“carp-like” mouth); antihelix of the ears is very prominent; varying degrees of intellectual disability and belligerent personality. Myelination abnormalities in the central nervous system.</td>
</tr>
</tbody>
</table>

### Table 81-13  
Microdeletion and Contiguous Gene Syndromes and Their Clinical Manifestations

<table>
<thead>
<tr>
<th>DELETION</th>
<th>SYNDROME</th>
<th>CLINICAL MANIFESTATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1p36</td>
<td>1p deletion</td>
<td>Growth restriction, dysmorphic features with midface hypoplasia, straight thin eyebrows, pointy chin, sensorineural hearing loss, progressive cardiomyopathy, hypothyroidism, seizures, intellectual disability</td>
</tr>
<tr>
<td>5q35</td>
<td>Sotos (50% are deletions of NSD1 gene in Asians but only 6% in whites)</td>
<td>Overgrowth, macrocephaly, prominent forehead, prominence of extraaxial fluid spaces on brain imaging, large hands and feet, hypotonia, clumsiness, mental disabilities</td>
</tr>
<tr>
<td>6p25</td>
<td>Axenfeld-Rieger</td>
<td>Axenfeld-Rieger malformation, hearing loss, congenital heart defects, dental anomalies, developmental delays, facial dysmorphism</td>
</tr>
<tr>
<td>7q11.23</td>
<td>Williams</td>
<td>Round face with full cheeks and lips, long philtrum, stellate pattern in iris, strabismus, supravalvular aortic stenosis and other cardiac malformations, varying degrees of intellectual disability, friendly personality</td>
</tr>
<tr>
<td>8p11</td>
<td>8p11</td>
<td>Kallmann syndrome 2 (hypogonadotropic hypogonadism and anosmia), spherocytosis (deletions of ankyrin 1), multiple congenital anomalies, intellectual disability</td>
</tr>
<tr>
<td>8q24.1-q24.13</td>
<td>Langer-Giedion or trichorhinophalangeal type II</td>
<td>Sparse hair, multiple cone-shaped epiphyses, multiple cartilaginous exostoses, bulbous nasal tip, thickened alar cartilage, upturned nares, prominent philtrum, large protruding ears, mild intellectual disability</td>
</tr>
<tr>
<td>9q22</td>
<td>Gorlin</td>
<td>Multiple basal cell carcinomas, odontogenic keratocysts, palmoplantar pits, calcification falx cerebri</td>
</tr>
<tr>
<td>9q34</td>
<td>9q34 deletion</td>
<td>Distinct face with synophrys, antverted nares, tented upper lip, protruding tongue, midface hypoplasia, conotruncal heart defects, intellectual disability</td>
</tr>
<tr>
<td>10p12-p13</td>
<td>DiGeorge 2</td>
<td>Many of the DiGeorge 1 and velocardiofacial 1 features (conotruncal defects, immunodeficiency, hypoparathyroidism, dysmorphic features)</td>
</tr>
<tr>
<td>11p11.2</td>
<td>Potocki-Shaffer</td>
<td>Multiple exostoses, parietal foramina, craniosynostosis, facial dysmorphism, syndactyly, intellectual disability</td>
</tr>
<tr>
<td>11p13</td>
<td>WAGR</td>
<td>Hypernephroma (Wilms tumor), aniridia, male genital hypoplasia of varying degrees, gonadoblastoma, long face, upward slanting palpebral fissures, ptosis, beaked nose, low-set poorly formed auncles, intellectual disability</td>
</tr>
<tr>
<td>11q24.1-11qter</td>
<td>Jacobsen</td>
<td>Growth restriction, intellectual disability, cardiac and digit anomalies, thrombocytopenia</td>
</tr>
<tr>
<td>15q11-q13 (paternal)</td>
<td>Prader-Willi</td>
<td>Severe hypotonia and feeding difficulties at birth, voracious appetite and obesity in infancy, short stature (responsive to growth hormone), small hands and feet, hypogonadism, intellectual disability</td>
</tr>
</tbody>
</table>
with moderate to mild intellectual disability and 0.5% of children with mild intellectual disability.

Clinical features (>30%) include short stature, microcephaly, hypertelorism, nose and ear abnormalities, and cryptorchidism. This group is also characterized by a family history of intellectual disability and an increased likelihood of restricted growth beginning in the prenatal period. Telomere mutations have also been associated with dyskeratosis congenita and other aplastic anemia syndromes as well as pulmonary or hepatic fibrosis. Both the subtelomeric rearrangements and the microdeletion and microduplication syndromes are typically diagnosed by molecular techniques like aCGH, FISH, and multiple ligation-dependent primer amplification. Recent studies show that aCGH can detect 14-18% of abnormalities in patients who are previously known to have normal chromosome studies.

**INSERTIONS**

Insertions occur when a piece of a chromosome broken at 2 points is incorporated into a break in another part of a chromosome. A total of 3 breakpoints are then required, and they can occur between 2 or within 1 chromosome. A form of nonreciprocal translocation, insertions are rare. Insertion carriers are at risk of having offspring with deletions or duplications of the inserted segment.
ISOCHROMOSOMES

Isochromosomes consist of 2 copies of the same chromosome arm joined through a single centromere and forming mirror images of one another. The most commonly reported autosomal isochromosomes tend to involve chromosomes with small arms. Some of the more common chromosome arms involved in this formation include 5p, 8p, 9p, 12p, 18p, and 18q. There is also a common isochromosome abnormality seen in the long arm of the X chromosome, and associated with Turner syndrome. Individuals who have 1 isochromosome within 46 chromosomes are monosomic for genes in the lost short arm and trisomic for the genes present in the long arm of the X chromosome.

MARKER AND RING CHROMOSOMES

Marker chromosomes are rare and are usually chromosome fragments that are too small to be identified by conventional cytogenetics; they usually occur in addition to the normal 46 chromosomes. Most are sporadic (70%); mosaicism is often (50%) noted because of the mitotic instability of the marker chromosome. The incidence in newborn infants is 1 in 3,300, and the incidence in persons with intellectual disability is 1 in 300. The associated phenotype ranges from normal to severely abnormal depending on the amount of chromosome material and number of genes associated with the fragment.

Ring chromosomes, which are found for all human chromosomes, are rare. A ring chromosome is formed when both ends of a chromosome are deleted and the ends are then joined to form a ring. Depending on the amount of chromosome material that is lacking or in excess (if the ring is in addition to the normal chromosomes), a patient with a ring chromosome can appear normal or nearly normal or can have intellectual disability and multiple congenital anomalies.

Marker and ring chromosomes can be found in the cells of solid tumors of children the cells of whose organs do not contain this additional chromosomal material.

Bibliography is available at Expert Consult.
Bibliography


81.4 Sex Chromosome Aneuploidy
Carlos A. Bacino and Brendan Lee

About 1 in 400 males and 1 in 650 females have some form of sex chromosome abnormality. Considered together, sex chromosome abnormalities are the most common chromosome abnormalities seen in liveborn infants, children, and adults. Sex chromosome abnormalities can be either structural or numerical and can be present in all cells or in a mosaic form. Those affected with these abnormalities might have few or no physical or developmental problems (Table 81-15).

TURNER SYNDROME

Turner syndrome is a condition characterized by complete or partial monosomy of the X chromosome and defined by a combination of phenotypic features (Table 81-16). Half of the patients with Turner syndrome have a 45,X chromosome complement. The other half exhibits mosaicism and varied structural abnormalities of the X or Y chromosome. Maternal age is not a predisposing factor for children with 45,X. Turner syndrome occurs in approximately 1 in 5,000 female live births. In 75% of patients, the lost sex chromosome is of paternal origin (whether an X or a Y). 45,X is one of the chromosome abnormalities most often associated with spontaneous abortion. It has been estimated that 95-99% of 45,X conceptions are miscarried.

Clinical findings in the newborns can include small size for gestational age, webbing of the neck, protruding ears, and lymphedema of the hands and feet, although many newborns are phenotypically normal (Fig. 81-17). Older children and adults have short stature and exhibit variable dysmorphic features. Congenital heart defects (40%) and structural renal anomalies (60%) are common. The most common heart defects are bicuspid aortic valves, coarctation of the aorta, aortic stenosis, and mitral valve prolapse. The gonads are generally streaks of fibrous tissue (gonadal dysgenesis). There is primary amenorrhea and lack of secondary sex characters. These children should receive regular endocrinologic testing (see Chapter 586). Most patients tend to be of normal intelligence, but intellectual disability is seen in up to 6% of affected children. They are also at increased risk for behavioral problems and deficiencies in spatial and motor perception. Guidelines for health supervision for children with Turner syndrome are published by the American Academy of Pediatrics and include pubertal induction, as well as treatment with growth hormone and oxandrolone.

Patients with 45,X/46,XY mosaicism, can have Turner syndrome, although this form of mosaicism can also be associated with male pseudohermaphroditism, male or female genitalia in association with...

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Karyotype</th>
<th>Approximate Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klinefelter syndrome</td>
<td>47,XXY</td>
<td>1/575-1/1,000 males</td>
</tr>
<tr>
<td>Other (48,XXYY; 49,XXXXY; mosaics)</td>
<td>1/50,000-1/80,000 male births</td>
<td></td>
</tr>
<tr>
<td>XYY syndrome</td>
<td>47,XXY</td>
<td>1/800,000 males</td>
</tr>
<tr>
<td>Other X or Y chromosome abnormalities</td>
<td>1/1,500 males</td>
<td></td>
</tr>
<tr>
<td>XX males</td>
<td>46,XX</td>
<td>1/20,000 males</td>
</tr>
<tr>
<td>Turner syndrome</td>
<td>45,X Variants and mosaics</td>
<td>1/1,500-1/5,000 females</td>
</tr>
<tr>
<td>Trisomy X</td>
<td>47,XXX</td>
<td>1/1,000 females</td>
</tr>
<tr>
<td>Other X chromosome abnormalities</td>
<td>1/3,000 females</td>
<td></td>
</tr>
<tr>
<td>XY females</td>
<td>46,XY</td>
<td>1/20,000 females</td>
</tr>
</tbody>
</table>

Table 81-16 Signs Associated with Turner Syndrome

- Short stature
- Congenital lymphedema
- Horseshoe kidneys
- Patella dislocation
- Increased carrying angle of elbow (cubitus valgus)
- Madelung deformity (chondrodysplasia of distal radial epiphysis)
- Congenital hip dislocation
- Scoliosis
- Widespread nipples
- Shield chest
- Redundant nuchal skin (in utero cystic hygroma)
- Low posterior hairline
- Coarctation of aorta
- Bicuspid aortic valve
- Cardiac conduction abnormalities
- Hypoplastic left-heart syndrome and other left-heart abnormalities
- Gonadal dysgenesis (infertility, primary amenorrhea)
- Gonadoblastoma (increased risk if Y chromosome material is present)
- Learning disabilities (nonverbal perceptual motor and visuospatial skills) (in 70%)
- Developmental delay (in 10%)
- Social awkwardness
- Hypothyroidism (acquired in 15-30%)
- Type 2 diabetes mellitus (insulin resistance)
- Strabismus
- Cataracts
- Red-green color blindness (as in males)
- Recurrent otitis media
- Sensorineural hearing loss
- Inflammatory bowel disease
- Celiac disease (increased incidence)

Figure 81-17 Redundant nuchal skin (A) and puffiness of the hands (B) and feet (C) in Turner syndrome. (From Sybert VP, McCauley E: Turner’s syndrome, N Engl J Med 351:1227–1238, 2004. Copyright © 2004 Massachusetts Medical Society.)
mixed gonadal dysgenesis, or a normal male phenotype. This variant is estimated to represent approximately 6% of patients with mosaic Turner syndrome. Some of the patients with Turner syndrome phenotype and a Y cell line exhibit masculinization. Phenotypic females with 45,X/46,XY mosaicism have a 15-30% risk of developing gonadal dysgenesis. The risk for the patients with a male phenotype and external testes is not so high, but tumor surveillance is nevertheless recommended. The American Academy of Pediatrics has recommended the use of FISH analysis to look for Y-chromosome mosaicism in all 45,X patients. If Y chromosome material is identified, laparoscopic gonadectomy is recommended.

Noonan syndrome shares many clinical features with Turner syndrome (old name was pseudo-Turner syndrome), although it is an autosomal dominant disorder resulting from mutations in several genes that are involved in the RAS-MAPK (mitogen-activated protein kinase) pathway. The most common of these is PTEN (50%), which encodes a protein-tyrosine phosphatase (SHIP-2) on chromosome 12q24.1. Other genes include SOS1 in 10-13%, RAF1 in 3-17%, KRAS <5%, BRAF <2%, and MAP2K <2%. Overlapping phenotypes are seen in LEOPARD (lentigines, electrocardiographic abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of genitalia, retardation of growth, deafness) syndrome, cardiofaciocutaneous syndrome, and Costello syndrome; these are Noonan-related disorders. Features common to Noonan syndrome include short stature, low posterior hairline, shield chest, congenital heart disease, and a short or webbed neck (Table 81-17). In contrast to Turner syndrome, Noonan syndrome affects both sexes and has a different pattern of congenital heart disease, typically involving right-sided lesions.

**KLINEFELTER SYNDROME**

Persons with Klinefelter syndrome are phenotypically male; this syndrome is the most common cause of hypogonadism and infertility in males and the most common sex chromosome aneuploidy in humans (see Chapter 583). Eighty percent of children with Klinefelter syndrome have a male karyotype with an extra chromosome X-47,XXX; the remaining 20% have multiple sex chromosome aneuploidies (48,XXXY; 48,XXYY; 49,XXXXY), mosaicism (46,XY/47,XXX), or structurally abnormal X chromosomes. The greater the aneuploidy, the more severe the mental impairment and dysmorphism. Early studies showed that the birth prevalence is approximately 1 in 1,000 males. The current prevalence of 47,XXX appears to have increased to approximately 1 in 580 liveborn boys; the reasons for this are still unknown. Errors in paternal nondisjunction in meiosis I account for half of the cases.

Puberty occurs at the normal age, but the testes remain small. Patients develop secondary sex characters late; 50% develop gynecomastia. They have taller stature. Because many patients with Klinefelter syndrome are phenotypically normal until puberty, the syndrome often goes undiagnosed until they reach adulthood, when their infertility aids in their clinical identification. Patients with 46,XY/47,XXX have a better prognosis for testicular function. Their intelligence shows variability and ranges from above to below average. Persons with Klinefelter syndrome can show behavioral problems, learning disabilities, and deficits in language. Problems with self-esteem are often the case with adolescents and adults. Substance abuse, depression, and anxiety have been reported in adolescents with Klinefelter syndrome. Those who have higher X chromosome counts show impaired cognition. It has been estimated that each additional X chromosome reduces the IQ by 10-15 points, when comparing these persons with their normal siblings. The main effect is seen in language skills and social domains.

**47,XXY**

The incidence of 47,XXY is approximately 1 in 800-1,000 males, with many cases remaining undiagnosed, because most affected individuals have a normal appearance and normal fertility. The extra Y is the result of nondisjunction at paternal meiosis II. Those with this abnormality have normal intelligence but are at risk for learning disabilities. Behavioral abnormalities including hyperactive behavior, pervasive developmental disorder, and aggressive behavior have been reported. Early reports that assigned stigmata of criminality to this disorder have long been disproved.

**Bibliography is available at Expert Consult.**

### Table 81-17 | Signs Associated with Noonan Syndrome

<table>
<thead>
<tr>
<th>Sign</th>
</tr>
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<tbody>
<tr>
<td>Short stature</td>
</tr>
<tr>
<td>Failure to thrive (use Noonan growth curve)</td>
</tr>
<tr>
<td>Tall forehead</td>
</tr>
<tr>
<td>Epicanthal folds</td>
</tr>
<tr>
<td>Ptosis</td>
</tr>
<tr>
<td>Blue-green irises</td>
</tr>
<tr>
<td>Hypertelorism</td>
</tr>
<tr>
<td>Low nasal bridge, upturned nose</td>
</tr>
<tr>
<td>Downward-sloping palpebral fissures</td>
</tr>
<tr>
<td>Myopia</td>
</tr>
<tr>
<td>Nystagmus</td>
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<tr>
<td>Low-set auricles</td>
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<tr>
<td>Dental malocclusion</td>
</tr>
<tr>
<td>Low posterior hairline</td>
</tr>
<tr>
<td>Short webbed neck (excessive nuchal skin), cystic hygroma</td>
</tr>
<tr>
<td>Shield chest</td>
</tr>
<tr>
<td>Pectus carinatum superiorly</td>
</tr>
<tr>
<td>Scoliosis</td>
</tr>
<tr>
<td>Pigmented vilonodular synovitis (polyarticular)</td>
</tr>
<tr>
<td>Cubitus valgus</td>
</tr>
<tr>
<td>Pulmonary valve stenosis (dysplastic valve)</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Atrial septal defect, ventricular septal defect</td>
</tr>
<tr>
<td>Lymphedema</td>
</tr>
<tr>
<td>Nevi, lentigines, café-au-lait spots</td>
</tr>
<tr>
<td>Cryptorchidism</td>
</tr>
<tr>
<td>Small penis</td>
</tr>
<tr>
<td>Delayed puberty</td>
</tr>
<tr>
<td>Bleeding disorders, including thrombocytopenia and factor deficiencies</td>
</tr>
<tr>
<td>Leukemia, myeloproliferative disorders, other malignancies</td>
</tr>
<tr>
<td>Cognitive delay (KRAS mutation)</td>
</tr>
</tbody>
</table>

### 81.5 Fragile Chromosome Sites

Carlos A. Bacino and Brendan Lee

Fragile sites are regions of chromosomes that show a tendency for separation, breakage, or attenuation under particular growth conditions. They appear as a gap in the staining. At least 120 chromosomal loci, many of them heritable, have been identified as fragile sites in the human genome (see Table 80-2).

One fragile site that has clinical significance is the one on the distal long arm of chromosome Xq27.3 associated with the fragile X syndrome. Fragile X accounts for 3% of males with intellectual disability. There is another fragile site on the X chromosome (FRAXE on Xq28) that has also been implicated in mild intellectual disability. The FRA11B (11q23.3) breakpoints are associated with Jacobsen syndrome (condition caused by deletion of the distal long arm of chromosome 11). Fragile sites can also play a role in tumorigenesis. CGG repeat expansion silences the gene producing fragile X mental retardation protein (FMRP) that regulates the translation of multiple mRNAs to specific proteins, thus affecting synaptic function. FMRP deficiency upregulates the metabotropic glutamate receptor (mGluR5) pathway. FMRP deficiency also alters the expression of matrix metalloproteinase (MMP) 9.

The main clinical manifestations of fragile X syndrome in affected males are intellectual disability, autistic behavior, macroorchidism, hyperextensible finger joints, and characteristic facial features (Table 81-18). Macroorchidism may not be evident until puberty. The facial features, which include a long face, large ears, and a prominent square jaw, become more obvious with age. Females affected with...
Bibliography


fragile X show varying degrees of intellectual disability and/or learning disabilities. Diagnosis of fragile X is possible by DNA testing that shows an expansion of a triplet DNA repeat inside the FMR1 gene on the X chromosome larger than 200 repeats. The expansion involves an area of the gene that contains a variable number of trinucleotide (CGG) repeats. The larger the triplet repeat expansion, the more significant the intellectual disability. In cases where the expansion is large, females can also manifest different degrees of intellectual disability. Males with premutation triple repeat expansions (50-200 repeats), have been found to have an adult, late onset progressive neurodegenerative disorder known as fragile X-associated tremor/ataxia syndrome.

Therapy of the diverse neuropsychiatric manifestations associated with fragile X syndrome is noted in Table 81-19. Inhibitors of the mGluR (overexpressed in fragile X) are undergoing clinical trials. In preliminary trials, minocycline (lowers MMP9) has resulted in short term improvements in anxiety, mood, and the clinical Global Impression Scale.

Bibliography is available at Expert Consult.

### 81.6 Mosaicism
Carlos A. Bacino and Brendan Lee

Mosaicism describes an individual or tissue that contains ≥2 different cell lines typically derived from a single zygote and the result of mitotic nondisjunction (see Fig. 81-1). Study of placental tissue from chorionic
Bibliography


Uniparental disomy (UPD) occurs when both chromosomes of a pair or areas from 1 chromosome in any individual have been inherited from a single parent. UPD can be of 2 types: uniparental isodisomy or uniparental heterodisomy. **Uniparental isodisomy** means that both chromosomes or chromosomal regions are identical (typically the result of monosomy rescue by duplication). **Uniparental heterodisomy** means that the 2 chromosomes are different members of a pair, both of which were still inherited from 1 parent. This results from a trisomy that is later reduced to disomy, leaving 2 copies from 1 parent. The phenotypical result of UPD varies according to the chromosome involved, the parent who contributed the chromosomes, and whether it is isodisomy or heterodisomy. Three types of phenotypic effects are seen in UPD: those related to imprinted genes (i.e., the absence of a gene that is normally expressed only when inherited from a parent of a specific sex), those related to the uncovering of autosomal recessive disorders, and those related to a vestigial aneuploidy producing mosaicism (see Chapter 80).

In uniparental isodisomy, both chromosomes or regions (and thus the genes) in the pair are identical. This is particularly important when the parent is a carrier of an autosomal recessive disorder. If the offspring of a carrier parent has UPD with isodisomy for a chromosome that carries an abnormal gene, the abnormal gene will be present in 2 copies and the phenotype will be that of the autosomal recessive disorder; the child has an autosomal recessive disorder even though only 1 parent is a carrier of that recessive disorder. It is estimated that all human beings carry approximately 20 abnormal autosomal recessive genes. Some autosomal recessive disorders like spinal muscular atrophy, cystic fibrosis, cartilage-hair hypoplasia, α and β-thalassemias, and Bloom syndrome have been reported in cases of UPD. The possibility of uniparental isodisomy should also be considered when a person is affected with >1 recessive disorder because the abnormal genes for both disorders could be carried on the same isodisomic chromosome. Uniparental isodisomy is a rare cause of recessively inherited disorders. Uniparental isodisomies can also be detected by SNP microarrays.

**Maternal UPD** involving chromosomes 2, 7, 14, and 15 and **paternal UPD** involving chromosomes 6, 11, 15, and 20 are associated with phenotypic abnormalities of growth and behavior. UPD of maternal chromosome 7 is associated with a phenotype similar to Russell-Silver syndrome with intrauterine growth restriction. These phenotypic effects may be related to imprinting (see under Imprinting, below) (Fig. 81-18).

UPD for chromosome 15 is seen in some cases of Prader-Willi syndrome and Angelman syndrome. In **Prader-Willi syndrome**, approximately 25-29% of cases have maternal UPD (missing the paternal chromosome 15). In **AngeImman syndrome**, paternal UPD of chromosome 15 is rarer and is observed in approximately 5% of the cases (missing the maternal chromosome 15). The phenotype for Prader-Willi syndrome (Fig. 81-19) and Angelman syndrome in cases of UPD is thought to result from the lack of the functional contribution from a particular parent of chromosome 15. In Prader-Willi syndrome the paternal contribution is missing, and the maternal contribution is missing in Angelman syndrome. Prader-Willi may be due to paternal deficiency of HB11-85 snoRNAs (small nucleolar RNAs). These findings suggest that there are differences in function of certain regions of chromosome 15, depending on whether it is inherited from the mother or from the father.

UPD most commonly arises when a pregnancy starts off as a **trisomic conception followed by trisomy rescue**. Because most trisomies are lethal, the fetus can only survive if a cell line loses 1 of the extra chromosomes to revert to the disomic state. One-third of the time, the disomic cell line is uniparental. This is the typical mechanism for Prader-Willi syndrome, and it is often associated with advanced maternal age. The embryo starts off as trisomy 15 secondary to maternal meiosis I nondisjunction, followed by random loss of the paternal chromosome. In this case, the disomic cell line becomes the more viable one and outgrows the trisomic cell line. When mosaic trisomy is found at prenatal diagnosis, care should be taken to determine whether UPD has resulted and whether the chromosome involved is one of the disomies known to be associated with phenotypic abnormalities. There must always be concern that some residual cells that are trisomic are present in some tissues, leading to malformations or

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**81.7 Chromosome Instability Syndromes**

Carlos A. Bacino and Brendan Lee

Chromosome instability syndromes, formerly known as chromosome breakage syndromes, are characterized by an increased risk of malignancy and specific phenotypes. They display autosomal recessive inheritance and have an increased frequency of chromosome breakage and/or rearrangement, either spontaneous or induced. They result from specific defects in DNA repair, cell cycle control, and apoptosis. The resulting chromosomal instability leads to the increased risk of developing neoplasms. The classic chromosome instability syndromes are Fanconi anemia, ataxia telangiectasia, Nijmegen syndrome, ICF (immunodeficiency, centromere instability, and facial anomalies) syndrome, Roberts syndrome, Werner syndrome, and Bloom syndrome.

**81.8 Uniparental Disomy and Imprinting**

Carlos A. Bacino and Brendan Lee

**Uniparental disomy** (UPD) occurs when both chromosomes of a pair or areas from 1 chromosome in any individual have been inherited from a single parent. UPD can be of 2 types: uniparental isodisomy or
dysfunction. The presence of aggregates of trisomic cells might account for the spectrum of abnormalities seen in persons with UPD.

**IMPRINTING**

Traditional genetics has for many years suggested that most genes are equally expressed when inherited from maternal versus paternal lineages. The only exception to this rule were genes on the X chromosome that are subject to inactivation, and the immunoglobulin genes subject to allelic exclusion, a phenomenon that results in monoallelic expression of a particular immunoglobulin chain by switching on and off expression of parental alleles. Genomic imprinting occurs when the phenotypic expression of a gene depends on the parent of origin for certain genes or in some cases entire chromosome regions. Whether the genetic material is expressed or not depends on the sex of the parent from whom it was derived. Genomic imprinting can be suspected in some cases on the basis of a pedigree. In these pedigrees, the disease is always transmitted from 1 sex and could be passed on silently to the opposite sex (Figs. 81-20 and 81-21).

Imprinting probably occurs in many different parts of the human genome and is thought to be particularly important in gene expression related to development, growth, cancer, and even behavior; over 60 genes have been classified as imprintable. Imprinting disorders may arise from UPD, deletions or duplications, epigenetic aberrant methylation patterns, or point mutations in a specific gene.

A classic example of imprinting disorder is seen in Prader-Willi syndrome and Angelman syndrome, 2 very different clinical conditions. These syndromes are usually associated with deletion of the same region in the proximal long arm of chromosome 15. A deletion on the paternally derived chromosome causes Prader-Willi syndrome, in which the maternally derived copy is still intact but some of the imprinted genes within this region normally remain silent. In contrast, a maternal deletion of the same region causes Angelman syndrome, leaving intact the paternal copy that in this case has genes that are also normally silent. In other situations, UPD can lead to the same diagnosis. Maternal UPD for chromosome 15 results in Prader-Willi syndrome due to lack of the paternal chromosome 15 contribution. In contrast, in Angelman syndrome, the UPD is always paternal, with no maternal contribution (Table 81-20). Many other disorders are associated with this type of parent of origin effect, as in some cases of Beckwith-Wiedemann syndrome, Russell-Silver syndrome, and neonatal diabetes.

**Bibliography** is available at Expert Consult.
Bibliography


Figure 81-19  
A and B, Individual showing morbid obesity with facial features as shown. C, Upper extremities are notable for small hands relative to body size. D, External genitalia after laparoscopic orchiopexy at 13 mo. Parental informed consent, as approved by the Baylor College of Medicine Institutional Review Board, was obtained to publish the photographs. (From Sahoo T, del Gaudio D, German JR, et al: Prader-Willi phenotype caused by paternal deficiency for the HBII-85 C/D box small nucleolar RNA cluster, Nat Genet 40:719–721, 2008.)

Figure 81-20 In this hypothetical pedigree suggestive of imprinting, phenotypic effects occur only when the mutated gene is transmitted from the mother, but not when it is transmitted from the father, that is, maternal deficiency. Equal numbers of males and females can be affected and not affected phenotypically in each generation. A nonmanifesting transmitter gives a clue to the sex of the parent who passes the expressed genetic information; that is, in maternal deficiency disorders (also termed paternal imprinting), there are "skipped" nonmanifesting females. This is theoretical, because in most clinical scenarios of maternal deficiency, such as Angelman syndrome, affected persons do not reproduce.
In theoretical pedigrees suggestive of paternal deficiency (maternal imprinting), phenotypic effects occur only when the mutated gene is transmitted from the father, but not when transmitted from the mother. Equal numbers of males and females can be affected and not affected phenotypically in each generation. In a theoretical situation, a nonmanifesting transmitter gives a clue to the sex of the parent who passes on the expressed genetic information; that is, in paternal deficiency (also known as maternal imprinting), there are “skipped” nonmanifesting males. In real-life clinical instances of Prader-Willi syndrome, affected persons do not reproduce.
Genetic studies are useful in diagnosing and treating rare pediatric conditions, often alleviating suffering, extending life, and, in the case of neonatal metabolic and presymptomatic screening, preventing injury before symptoms develop. Genetic studies can also contribute to the understanding of more common diseases, such as asthma and diabetes. An understanding of the complex and potentially multiple pathways leading to disease is crucial for the development of new therapies and prevention strategies.

Common pediatric diseases are often multifactorial, and the combination of many genes and environmental factors triggers a complex sequence of events leading to disease. Each individual has variations in his or her set of genes; the cumulative effect of the individual's gene variants with each other and with the environment influence susceptibility to disease, response to various medications, and susceptibility to specific drug toxicities. The complexity of the combination of contributing factors increases the challenge of finding genetic variants that cause disease. Genetic tools include the completed human genome sequence, public databases of genetic variants, and the human haplotype map. In addition to public genetic databases, dramatic reduction in the cost of genotyping and DNA sequencing has allowed very large numbers of genetic variants to be efficiently tested in large numbers of patients. Most of these studies focus on common variants (those with frequencies >5%). New technologies for DNA sequencing are already allowing whole exome sequencing in many individuals at very low cost. This technology is being used to investigate the role of rare coding sequence variants in common diseases. The incorporation of these tools into large, well-designed population studies is the field of genetic epidemiology. Many new methods for analyzing genetic data have been developed, stimulating a renaissance in applied population genetics. So far, these methods of investigation have been used less extensively in pediatric diseases than in adult-onset conditions. This is a consequence of the relative lack of large-scale DNA sample sets for many common diseases of children.

We can now project that in the near future it will become routine to carry out “genomic profiling” by one technique or another for individual children. These methods will find clinical utility in decision algorithms for disease screening and initiation of treatment, drug selection, and targeted preventive strategies. The results will be of an unprecedented complexity, so that physicians and parents will increasingly rely on the coupling of genetic data to clinical decision support tools linked to the electronic health record.

82.1 Major Genetic Approaches to the Study of Common Pediatric Disorders

John W. Belmont and Brendan Lee

Figure 82-1 shows a model for the genetic contribution to health. Genetic variation that can have an impact on disease susceptibility is present in every person. Sometimes single-gene mutations cause a condition, as is the case for cystic fibrosis or sickle cell anemia. But other kinds of genetic variations can contribute much less strongly to the emergence of specific medical conditions, and the effect can depend upon exposure to certain environmental factors. One goal in medical genetics is to identify genes that contribute to disease in the hope of preventing the occurrence of disease, either by avoiding inciting environmental factors or by instituting interventions that reduce risk. For persons who cross the threshold of disease, the goal is to better understand the pathogenesis in the hope that this will suggest better approaches to treatment. Common genetic variation can also influence response to medications and the risk of toxicities of various medications and environmental toxins.
Complex traits may be inherently difficult to study if there are problems with the precision of clinical diagnosis. This is particularly true of neurobehavioral traits. A starting point in the genetic analysis of a complex trait is to obtain evidence in support of a genetic contribution and to estimate the relative strength of genetic and environmental factors. Complex traits typically exhibit familial clustering, but are not transmitted in a regular pattern like autosomal dominant or recessive inheritance. Complex traits often show variation among different ethnic or racial groups, possibly reflecting the differences in gene variants among these groups.

Assessing the potential genetic contribution begins by determining whether the trait is seen among related individuals more often than in the general population. A common measure of familiality is the first-degree relative risk (usually designated by the symbol λr), which is equal to the ratio of the prevalence rate in siblings and/or parents to the prevalence rate in the general population. For example, the λr for type 1 diabetes is about 15. The relative strength of genetic and non-genetic risk factors can be estimated by variance components analysis, and the heritability of a trait is the estimate of the fraction of the total variance contributed by genetic factors (Fig. 82-2).

It is not uncommon for a minority of cases of common diseases like diabetes to be caused by single-gene mutations (mendelian inheritance), chromosomal disorders, and other genomic disorders. These less-common causes of the disease can often provide important insight into the most important molecular pathways involved. Chromosomal regions with genes that might contribute to disease susceptibility could theoretically be located with linkage mapping, which locates regions of DNA that are inherited in families with the specific disease. But practically, this has turned out to be quite difficult for most complex traits either because of a dearth of families or because the effect of individual genetic loci is weak.

Genetic association studies are more powerful in identifying common gene variants (>5% in the population) that confer increased risk of disease, but they fail if the disease-causing gene variants are relatively rare. Detection of the modest effect of each variant and interactions with environmental factors requires well-powered studies that often include thousands of subjects. A number of parallel approaches for analyzing the aggregate effects of rare variants in genes have also been developed. Such rare variant association methods also seem to require large sample sizes because the gene effects have also proven to be relatively weak.

Linkage mapping and association studies require markers along the DNA that can be ascertained, or genotyped, with large-scale, high-throughput laboratory techniques. Markers that are typically used are in the forms of microsatellites and single-nucleotide polymorphisms (SNPs; Fig. 82-3). Although humans all have the same genetic material, each person's genome is slightly different. A sample of the same region of genome from 50 people will reveal that approximately 1 in every 200 bases varies from the more common form. Although most SNPs lack any obvious function, a few alter the amino acid sequence of the protein or affect regulation of gene expression. Some of these functional alterations directly affect susceptibility to disease. A complex clinical phenotype can be defined by the presence or absence of a disease as a dichotomous trait, or by selection of a clinically meaningful variable such as serum glucose in type 2 diabetes, which is a continuous or quantitative trait.

Although it might not be possible to define subgroups of patients in advance based on common disease mechanisms, the more uniform the phenotype, the more likely that a genetic study will be successful. Locus heterogeneity refers to the situation in which a trait results from the independent action of more than 1 gene. Allelic heterogeneity indicates that more than 1 variant in a particular gene can contribute to disease risk. The development of a trait or disease from a nongenetic mechanism results in a phenocopy. These 3 factors often contribute to the difficulty in identifying individual disease susceptibility genes because they reduce the effective size of the study population.

A person bearing any variant or allele (inherited unit, DNA segment, or chromosome) in a gene has a certain probability of being affected with a specific gene variant-associated disease. This is called the

![Figure 82-2 Heritability concept. The phenotypic variance of a particular trait can be partitioned between the contributions of the genetic variance, the environmental variance, and the measurement variance. This is usually empirically determined. Heritability is defined by the proportion of the phenotypic variance that is accounted for by the genetic variance. One can estimate the heritability from correlation of a quantitative trait between relatives.](image1)

![Figure 82-3 Different combinations of SNPs are found in different individuals. The locations of these SNPs can be pinpointed on maps of human genes. Subsequently, they can be used to create profiles that are associated with difference in response to a drug, such as efficacy and nonefficacy.](image2)
penetrance. Some diseases manifest signs only later in life (age-related penetrance), which could lead to misclassifying children who actually have the disease-producing gene as unaffected. Single-gene disorders are typically caused by mutations with relatively high penetrance, but some common variants have very low penetrance because their overall contribution to the disease is small. Many such common variants can contribute to disease risk for a complex trait. For example, normal human height is influenced by more than 400 genes.

Ideally, important environmental exposures should be measured and accounted for in a population because there may be a dependent interaction between the environmental factor and specific genetic variant. An example is the likely requirement for a viral infection preceding onset of type 1 diabetes. Although gene X environment interactions are strongly suspected to play an important role in common diseases, it is difficult to identify and measure them. Very large studies with uniform collection of information about environmental exposures are rare. New methods, such as genome-wide analysis of DNA methylation, may show evidence of environmental effects—so-called developmental programming. This information might be used to discover and validate gene-environment interactions.

LINKAGE MAPPING
Linkage studies were used in the past to isolate genes that cause rare genetic syndromes; modified methods have been used to identify chromosomal regions linked to more common diseases. Linkage studies involve tagging segments of a person's genome with markers that allow identification of segments that have been inherited through the family along with disease. The markers are typically microsatellites or SNPs that define and help to distinguish which type of an allele any person carries. The type of an allele is referred to as a genotype. Linkage analyses of common diseases have shown inconsistent results. Factors such as heterogeneity, pleiotropy, variable expressivity, and reduced penetrance, in addition to variability in environmental exposures, weaken the power of linkage studies in complex traits.

GENETIC ASSOCIATION
For multifactorial common diseases, association analyses may be used to identify causally important genes. There are two types of association study: direct association, in which the causal variant itself is tested to see whether its presence correlates with disease, and indirect association, in which markers that are physically close to the biologically important variant are used as proxies. The correlation of markers with other genetic variants in a small region of the genome is called linkage disequilibrium. Indirect association is enabled by the construction of a detailed genetic map in 3 reference populations (Europeans, Asians, West Africans) through the International HapMap Project. SNPs that tag most of the genome have been identified and can be genotyped at low cost using specially designed microarrays.

Three basic study designs are used for association testing: a case-control design, in which the frequency of an allele in the affected group is compared with the unaffected group; a family-based control design, in which parents or siblings of an affected individual are used as the controls; and a cohort design, in which large numbers of subjects are ascertained and then followed for the onset of any number of diseases. The cohort analysis is very expensive and there are few true cohort studies.

Family-based control study designs are somewhat attractive for pediatric diseases because it is usually possible to enroll parents. These studies solve a major problem in testing for association because the parents are perfectly matched for genetic background. When parents are collected, the statistical test used for these studies is called the transmission disequilibrium test (TDT). TDT compares the transmitted genotype with the inferred nontransmitted genotype. The success of all association analysis depends on the design of a well-powered study, with enough subjects, and an accurately measured trait to avoid phenotypical misclassification. In large, population-based studies, confounding by ethnicity or population stratification could distort results. Some genetic variants are more common in people from a particular ethnic group, which could cause an apparent association of a variant with a disease, when the disease rate happens to be higher in that group. This association would not be a true association between an allele and a disease, because the association would be confounded by genetic background. The family-based tests using the TDT are immune to population stratification. However, TDT and related study designs are inherently less efficient than case-control studies. Newer methods for measuring subtle mismatching between cases and controls using many thousands of markers routinely genotyped in genome-wide association studies allow this effect to be accounted for.

Association studies should be a powerful tool to find genetic variation that confers risk to an individual; the effect of any one genetic variant will be a very small contribution to the complex disease pathway. Genetic variants have been found that implicate a novel gene in a process, motivating more in-depth research into systems that will affect disease outcome. Associations such as the ApoE4 variant with an increased risk of Alzheimer disease are noted by many studies. Many published association results are not reproducible; insufficient power and stratification might account for the inconsistencies. As of early 2014, more than 6000 disease associations for more than 600 medically important traits have been discovered and replicated in large studies.

New low-cost methods for sequencing the complete exomes and genomes of individuals will soon allow a more comprehensive evaluation of the full range of genetic variants involved in common diseases. The goal of the $1000 genome once seemed distant but may be achieved very soon. Rare genetic variants, including small insertions or deletions, could turn out to be extremely important in explaining the impact of genetic factors in important pediatric diseases such as autism, cardiovascular malformations, and other birth defects. Common traits such as obesity, diabetes, and autoimmune diseases might also be affected by rare variants. In common severe disorders like intellectual disability and complex heart malformations, de novo mutations (i.e., mutations not present in either parent) are likely to play an important role.

Bibliography is available at Expert Consult.
Bibliography
Chapter 83
Genetic Approaches to Rare and Undiagnosed Diseases
William A. Gahl, David R. Adams, Thomas C. Markello, Neal F. Boerkoel, and Cynthia J. Tifft

Rare and novel disorders often present in childhood and represent a diagnostic challenge that can be addressed using advanced genetic techniques.

SCOPE OF GENETIC DISEASE
An estimated 7000 rare disorders are recognized, and the existence of approximately 23,000 human genes suggests that many more genetic diseases will be discovered in the future. These genetic diseases comprise a set of maladies amenable to a variety of diagnostic approaches. Knowledge about the human genome creates a new opportunity to diagnose extremely rare disorders and discover new diseases. One
approach was taken by the National Institutes of Health (NIH) Undiagnosed Diseases Program (UDP).

Potential reasons patients may remain undiagnosed despite intensive prior investigation include:
- The genetic mutation had not previously been associated with the disease phenotype
- There is allelic heterogeneity (same gene but different mutation producing a different phenotype)
- There is locus heterogeneity (different genes producing similar phenotype)
- Presentation of monosymptomology or unusual features of a polysymptomatic or rare disease

The 3,000 patient applications to the UDP have involved collaboration between the referring healthcare team and the NIH group. Prior investigations are recounted in a summary letter from the referring clinician and documented with medical records that include photos, videos, imaging and histologic slides of biopsy material. Specialty consultants review the records and the UDP directors determine the next steps. The patients who are accepted come to the Clinical Center for a week-long inpatient admission. Approximately half of the patients with undiagnosed diseases have neurological disease; cardiovascular, rheumatology, immunology, and pulmonary problems are also frequent. Approximately 40% of accepted patients are children, among whom unknown multiple congenital anomalies and neurologic disorders are common.

**CLINICAL EVALUATION**

The term undiagnosed refers to patients who remain without a definitive diagnosis after an extensive workup. This occurs in part because every individual has a unique genetic and environmental background, and diseases express themselves in an unlimited number of ways. Undiagnosed conditions include those that have never been seen by the diagnostician, unusual presentations of otherwise recognizable conditions, and combinations of conditions that obfuscate each other’s identities. A thorough clinical investigation allows the clinician to broaden the differential diagnosis through research, consultation, clinical testing and consideration of atypical presentations of previously known diseases. Extensive phenotyping, imaging, and other tests provide better documentation of the presentation and make the case available for association with future newly discovered diseases, genetic variants, and patient cohorts.

A complete history anchors the data, and includes prenatal and neonatal findings, developmental milestones, growth pattern, onset and progression of symptoms and signs, precipitating influences, response to medications, and a pedigree to determine which family members are affected. Pertinent physical findings include dysmorphism, organomegaly, neurologic impairment, bone involvement, and dermatologic findings. Because many rare and novel disorders are multisystemic, consultants play a critical role in every diagnostic evaluation. Typical studies performed to address possible diagnoses are listed in Table 83-1. The evaluation of a pediatric neurology case involves even more extensive studies (Table 83-2).

An inpatient admission allows for close interaction among experts in different fields, informs the workup of complex cases, and often leads to a focus on the discovery of a new disease. In that situation, other family members need to be evaluated to definitively ascertain whether they are affected with the disorder under consideration.

**AVAILABLE COMMERCIAL LABORATORY GENETIC STUDIES**

Once phenotyping is complete, a differential list of genetic disorders can be compiled. Laboratory molecular testing is available for an increasingly large spectrum of molecular disorders. In many cases, several related diseases are included in a panel of molecular tests. Examples include X-linked cognitive impairment, hereditary spastic paraplegia, spastic paraplegia and gait, spinocerebellar ataxias, dystonias, and mitochondrial disorders. Some of these individual tests and panels are expensive, and added together they may exceed the cost of exome sequencing.

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**Table 83-1 Initial Studies to Generate New Diagnostic Hypotheses**

<table>
<thead>
<tr>
<th>TEST(S)</th>
<th>RELATED DISORDERS/ DISORDER GROUPS</th>
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<tr>
<td>Electrolytes, lactate, pyruvate</td>
<td>Energy disorders, including mitochondrial disorders</td>
</tr>
<tr>
<td>Plasma amino acids</td>
<td>Renal disorders, amino acid disorders</td>
</tr>
<tr>
<td>Urine organic acids</td>
<td>Renal disorders, organic acid disorders</td>
</tr>
<tr>
<td>Aldolase, creatine phosphokinase</td>
<td>Muscle disorders</td>
</tr>
<tr>
<td>Carnitine (free, total, acyl,</td>
<td>Fatty acid oxidation disorders, carnitine metabolism disorders</td>
</tr>
<tr>
<td>panel)</td>
<td></td>
</tr>
<tr>
<td>Cerebrospinal fluid (CSF) analysis</td>
<td>Neurotransmitter disorders, inborn errors of metabolism, select disorders that may present only in the CSF</td>
</tr>
<tr>
<td>Brain MRI/magnetic resonance spectroscopy</td>
<td>Structural clues to disorders affecting central nervous system</td>
</tr>
<tr>
<td>Mass spectrometry to detect N- and O-linked proteoglycan abnormalities</td>
<td>Congenital disorders of glycosylation</td>
</tr>
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<td>Lysosomal enzyme testing</td>
<td>Lysosomal storage diseases</td>
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<td>White cell and skin electron microscopy</td>
<td>Lysosomal storage diseases; neuronal lipofuscinoses</td>
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<td>Pathologic evaluation of affected tissues with special stains, DNA hybridization</td>
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<td>Single-nucleotide polymorphism/exome/ genome/karyotype</td>
<td>Any</td>
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<tr>
<td>Erythrocyte sedimentation rate, C-reactive protein</td>
<td>Inflammatory disorders</td>
</tr>
</tbody>
</table>

**SINGLE-NUCLEOTIDE POLYMORPHISM ARRAYS**

There are 2 technologies that are cost-effective for medical uses and can examine the entire genome with resolution at the level of a single base pair. These are single-nucleotide polymorphism (SNP) arrays (microarrays or chips) and next-generation sequencing. The human genome’s 3.2 billion bases include many that are polymorphic. Polymorphisms are bases that are not the usual one at a defined position and yet occur with a frequency of >1% within a given population. For any 2 individuals who are not closely related, there are approximately 2.5 × 10^6 SNPs that vary between them (and between each individual and the canonical human reference), or about 1 polymorphism for every 1,000 bases in the genome on average. Within a single ethnic population there is about 1 common SNP per 3,000-7,000 bases, where common means a greater than 10% chance that any 1 patient will be polymorphic (heterozygous) at that position. A few hundred thousand to a few million of these common SNPs can be included on a DNA hybridization array and examined simultaneously in a single laboratory test. This technique produces genome-wide results that reveal copy number variations; mosaicism is also revealed, as are regions of...
identity by descent. These results are very useful in complementing the next-generation sequencing results. One example of this is the use of the SNP deletion regions to denote where to look for a point mutation in the next-generation sequence of the child (to detect the compound heterozygous recessive pairing of a deletion with a point mutation).

**EXOME SEQUENCING**

Technical advances have allowed for massive DNA sequencing at a reasonable price, making it feasible to determine the sequence of the coding regions of almost all of the human genes. Because this involves 1.7% of the 3.2 billion bases in the human genome, **exome sequences** comprise approximately 60,000,000 bases. These satisfactorily cover 80–85% of the known genes, and are determined by sequencing short “reads” (DNA fragments) and aligning them to a composite reference sequence of the human genome. In part because of SNP interference with hybridization, ambiguities in alignment, and chemistry error rates, the average exome has about 20,000 bases (0.03%) that differ from the “reference” sequence and from any other single, unrelated human sequence of the same ethnic group. Most of these variants are inconsequential polymorphisms. The problem is that each of the 20,000 variants of unknown significance is a potential disease-causing variant, yet only 1 is the disease-causing mutation for a monogenic disorder (with perhaps 2 or 3 additional loci modifying severity). The task of the clinician is to reduce the credible variants from 20,000 to a manageable number, such as 5.

This process involves using “filters,” or programs that eliminate false-positive variants without eliminating the true variants. The single best filter uses the exome sequencing (ES) of nuclear family members (i.e., parents and siblings), but only if their true affected or unaffected status is certain. If, for example, an unaffected sibling’s gene has 2 variants on opposite alleles that are the same as those of the affected proband, then those variants can be eliminated as causing the proband’s disease. This emphasizes the importance of collecting family DNA and obtaining a very careful evaluation of family members. In general, having the proband, both parents and siblings provides sufficient power to reduce the candidate variants to a reasonable number for all mendelian inheritance models, assuming complete penetrance.

As an example, if autosomal recessive inheritance is postulated, then the ES analysis should require mutations on both alleles of the proband, with 1 of the 2 mutations present in 1 parent and the other
mutation present in the other parent. Affected sibs must have both mutations, and unaffected sibs must have either 1 or none. Software programs have succeeded using a homozygous recessive model, and for significantly deleterious variants, using a compound heterozygous recessive model.

Base changes that result in amino acid changes (missense mutations) are evaluated by programs that gauge the pathogenicity of the change. This involves estimates of how tightly the base is conserved over evolution, whether the amino acid change charge, size, or conformation, and, sometimes, where in the protein the amino acid change resides. Analyzing how changes in the gene's code influence protein function remains an inexact science, but approximations have been used with some success. Software programs, including PolyPhen-2, SIFT, and MutationTaster, rate the pathogenicity of amino acid changes. In addition, evolutionary consistency of a base can be evidence of deleteriousness of a change in that base, even if it is not involved in an amino acid change (promoter binding domains, methylation sites). Finally, some filters compare variants to databases that list changes considered to be benign (database of single-nucleotide polymorphisms), known to cause diseases other than those under investigation, or simply found frequently in many random genomes (1000 Genomes). These databases can be very helpful, but they are not entirely reliable because their entries have not been curated in all cases to a medically useful level of confidence.

The analysis of exome sequences is advancing rapidly, based upon the development of new filters and larger, better, and more informative databases. However, several key points need to be considered when employing genome-scale sequencing for clinical diagnostics.

Positive predictive value gives the likelihood that a positive test is a true positive. This is higher in a population in which a disease is frequent and lower in a population where the disease is rare. A person being tested with ES will show no clinical signs or symptoms of most of the genetic diseases for which the ES tests. Therefore, many apparently positive findings will be false positives. This manifests as the frequent occurrence of DNA variations in genes that are associated with phenotypes that do not match the person being tested. Such variants are difficult to interpret.

Individual versus family studies are relevant, as family data allow for variants to be substantially filtered. This advantage must be weighed against the financial costs of studying families versus individuals. Furthermore, family studies are useless if an affected person is called unaffected or vice versa. Therefore, phenotyping family members is critical. For later-onset conditions, younger siblings may not be suitable for inclusion in an exome study unless their affected status can be determined unambiguously.

Data revisiting policies must be addressed. Genome-scale sequencing generates data for many genes beside those involved in the current diagnostic effort. The sequencing data are of potential use in the future care of the patient. Even though some mutated genes are not reported because they are not currently associated with any medical condition, future advances may implicate such a gene in a human disease. The person ordering the exome study should be aware of the data reuse policy of the testing facility. In the current testing environment, time-limited data reuse and/or reuse fees are increasingly common.

Early discussion with a genetic specialist is critical. Genetic counseling should be sought before an exome study is sent rather than after the results become available. Proper consent for exome studies is an involved process, including information about disease risk factors, unrelated medical conditions, carrier states and cancer susceptibility. Consented individuals should be given the opportunity to consider which types of results they would like to have returned.

Anticipating findings that are difficult to use clinically is an important part of counseling. The problem of variants of unknown significance is well known for any type of genetic testing. Genome-scale sequencing amplifies this problem to include a wide variety of results that are difficult to use for medical decision making. Depending on the breadth of analysis and the resulting clinical report, different numbers of such findings will be returned to the ordering physician. Discussing such variants with families can be difficult; counseling families about the likelihood of receiving this type of result before testing is performed can help the family to cope when the report is returned (see Chapter 77).

When used as a gene panel, ES rules in but does not rule out. An exome study is a cost-effective way to test many genes at one time. However, there can be variation in coverage of any given exon among exome datasets. Therefore, even though exome studies are a powerful tool for variant discovery, they are not always sufficient to exclude variants in a panel of genes. With careful analysis involving laboratory validation on many similarly processed individuals, the exome coverage of any given gene can be assessed. However, commercial/clinical testing facilities may be unwilling to perform such an analysis when a large set of genes needs to be considered. Therefore, there is still a role for the use of a gene panel when the index of suspicion is high for a disorder caused by 1 of a large group of genes. Cerebellar ataxia and hereditary spastic paraparesis are examples.

Providing information to the testing facility improves the chances of a diagnosis. ES interpretation will benefit substantially from the incorporation of accurate and detailed clinical information about the presenting phenotype. The more clinical information that is provided to the testing lab, the more specific and useful the clinical report will be.

GENE FUNCTION STUDIES

Despite filtering for frequency and predicted deleteriousness, a variant identified by genomic sequencing cannot be interpreted as the cause of an individual’s disease unless it has been previously demonstrated to cause a disease with a similar phenotype. To prove causality, medical genetics relies upon association (the recurrence of mutations within a gene among individuals with a similar phenotype). For rare diseases, there may be too few affected patients to demonstrate a statistically-significant association. In this setting, other evidence will be required to connect a specific genetic variant with an isolated phenotype. One approach is to accumulate additional diagnostic data about the patient that can be used to prioritize genetic variants (phenotype ontologies, metabolomics, glycomics, proteomics, and lipidomics). A second approach is to develop models that recapitulate the disease in question, such as mice, zebrafish, fruit flies, yeast, and cultured cells. Third, the variant in question can be linked to a biologic process or pathway that is known to cause a similar phenotype when disturbed. Finally, standardized and correlated phenotypic and genomic data are deposited into a database to identify other individuals with a similar phenotype and mutations in the same gene.

Physicians may apply their past biases to a group of variants that could be disease causing, but this is often misleading. A standardized computational approach would be preferable. For example, the Human Phenotype Ontology will standardize the description of a disease and, because the descriptors have been mapped to other human diseases and to mutant model organisms, will identify possible candidate genes and genetic networks for causing the disease. Similarly, untargeted laboratory screening tests provide an unbiased survey of patient cellular biology and physiology and a more informed prioritization of variants causing the patient’s disease.

The ultimate proof of causality is to ameliorate the disease process by correcting the genetic defect, and this can sometimes be demonstrated in a model system that recapitulates the human disease. If model systems fail to identify the genetic cause of an individual’s disease, one must search for other patients with a similar phenotype and mutations in the same gene. This can be accomplished using public databases that are interpreted using strict statistical and biologic standards.

PEDIATRIC ISSUES

During its first 4 yr, the UDP at NIH received 500 pediatric applications. In >10% of cases, more than 1 family member, usually a sibling, was similarly affected. There were 2 peaks in the age distribution of the children: 1 at 4–5 yr, reflecting patients with congenital disorders, and 1 at 16–18 yr representing disorders with symptom onset at early school age. The majority of applicants had been on a diagnostic odyssey for more than 5 yr. Of the 200 pediatric cases accepted, 175 were
evaluated to date and 25% received a diagnosis. Of the diagnoses, half were obtained using conventional diagnostic methods, including clinical suspicion with molecular confirmation, biochemical testing with molecular confirmation, or radiographic interpretation. In the remainder of cases the diagnosis was arrived at using SNP analysis and next-generation sequencing; all of these were rare diseases.

Pediatric medical records require attention to what has and what has not been completed previously. The electronic medical record is an important tool for medical practice, but copy forward functions can perpetuate errors, such as reports of normal testing when in fact the test was recommended or ordered but cancelled. Repetitive copying also fosters sloppiness in critical thinking, failure to take an adequate history, and missing the nuances of symptom progression. A history and physical examination should be performed anew and all prior testing results confirmed via copies of original laboratory reports.

Prolonged and painful procedures should be performed under sedation, but the risks associated with sedation must be weighed against the value of the information and samples to be obtained (see Table 83-2).

CONSIDERATIONS FOR FAMILIES OF UNDIAGNOSED CHILDREN

When a child comes to a genetics clinic for evaluation the parents want to know:

- What does my child have? (diagnosis)
- Why did it happen? (etiology/inheritance)
- What will happen in the future? (natural history)
- Is there a treatment? (therapy)
- Could the same thing happen to other family members? (recurrence risk)

The answers to all of these questions require an accurate diagnosis. The lack of a diagnosis also makes both the family and the physician uncomfortable, raises suspicion among relatives and acquaintances, and creates feelings of guilt about not having worked hard enough to find a diagnosis. As a consequence, families consult more and more specialists, and are often frustrated with the lack of coordination among providers. It is helpful for the family to save copies of every test and every visit from each institution and compile them in a binder for travel among institutions. A 2-3 page narrative summarizing the child’s history, medications, list of healthcare providers with contact information, main medical issues, level of functioning on well days and sick days, and interventions that worked in the past, can be invaluable in an emergency room setting. An electronic copy is easily updated. Parents can always be the best advocates for their child, particularly an undiagnosed child.

Recommendations to parents of an undiagnosed child are similar to those that apply to any child with chronic illness:

- Keep copies of all records, electronic and otherwise, and organize them routinely, especially copies of original reports from “send-out” labs.
- Carry an updated emergency letter.
- Establish a medical home even if you obtain many second opinions.
- Find a physiatrist (rehabilitation medicine physician) to coordinate rehabilitative care.
- Be aggressive with the school system about services using, a legal advocate if necessary.
- Explore parent support groups for unknown disorders ( Syndromes Without a Name, National Organization for Rare Disorders).

- Periodically check with providers (especially geneticists) for new diagnoses reported in the medical literature.
- Carve out time for yourselves as caregivers by engaging extended family members or respite care services.
- Work at supporting and being attentive to well children in the family.
- For the very sick dying child, consider an autopsy as a final attempt to establish a diagnosis especially when there is a possibility of future pregnancies.

THE DIAGNOSTIC SPECTRUM

The extent of determining the diagnosis varies considerably, from that of recognizing a clinical entity, to a largely molecular diagnosis, or to one in which the entire pathogenesis is known. In addition to known disorders, SNP and ES analyses may also identify variants in genes that are candidates for causing a new disease.

One example of a diagnosis involves 2 brothers whose parents were first cousins. The brothers had an early-onset spastic ataxia-neuropathy syndrome, with lower-extremity spasticity, peripheral neuropathy, ptosis, oculomotor apraxia, dystonia, cerebellar atrophy, and progressive myoclonic epilepsy. A homozygous missense mutation (c.1847G>A; p.Y616C) in AFG3L2, which encodes a subunit of a mitochondrial protease, was identified by ES. The AFG3L2 protein can bind to another AFG3L2 molecule or to paraplegin. UDF collaborators in Germany used a yeast model system to demonstrate that the patients’ mutation affects the specific amino acid involved in the formation of both of these complexes. As a result, the brothers exhibited the signs and symptoms of a known AFG3L2 defect, autosomal dominant spinocerebellar ataxia type 28 (SCA28), and a known paraplegin defect, hereditary spastic paraplegia type 7 (SPG7). Other features of a mitochondrial disorder (oculomotor apraxia, extrapyramidal dysfunction, myoclonic epilepsy) were also present. The 2 brothers represent the first such cases in the world, and expand the phenotype of AFG3L2 disease.

A second example involves 2 siblings ages 5 and 10 yr with hypotonia, developmental delays, facial dysmorphisms, hearing loss, nystagmus, seizures, and atrophy on brain MRI. In this case, the leading clue was biochemical in nature, and genetic analysis confirmed the diagnosis. Urine thin-layer chromatography for oligosaccharides identified a strong band determined by mass spectrometry to consist of a tetrasaccharide containing 3 glucose and one mannose. This suggested a defect of glucosidase I, the first enzyme involved in endoplasmic reticulum trimming of N-linked glycoproteins from a high-mannose to a complex form. Mutation analysis confirmed compound heterozygous mutations in the glucosidase I gene, establishing the diagnosis of congenital disorder of glycosylation IIb; the 2 siblings were the second and third patients in the world with this disorder.

The genetic analysis of rare and undiagnosed diseases has also yielded a variety of unique phenotypes that very likely represent new diseases. When variants in multiple genes are candidates for causing such a disorder, functional studies are required to demonstrate causality. This was successfully accomplished for a new disorder of vascular calcification identified and elucidated through the UDP at the NIH and found to be caused by a genetic deficiency of CD73, an enzyme on the surface of vascular cells that converts adenosine monophosphate to adenosine and inorganic phosphate.

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Online Mendelian Inheritance in Man, OMIM: McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD). http://omim.org/.
Many childhood conditions are caused by single-gene mutations that encode specific proteins. These mutations can result in the alteration of primary protein structure or the amount of protein synthesized. The function of a protein, whether it is an enzyme, receptor, transport vehicle, membrane component, or structural element, may be compromised or abolished. These hereditary biochemical disorders are termed \textit{inborn errors of metabolism} or \textit{inherited metabolic disorders}.

Most mutations are clinically inconsequential and represent polymorphic differences that set individuals apart (\textit{genetic polymorphism}). Some mutations produce disease states that range from very mild to lethal. Severe forms of these disorders usually become clinically apparent in the newborn period or shortly thereafter.

**COMMON CHARACTERISTICS OF GENETIC DISORDERS OF METABOLISM**

Although the manifestations of genetic metabolic disorders are quite variable, the following features are shared among most of these conditions:

1. The affected infant is normal at birth and becomes symptomatic later on in life. This differentiates these infants from those who appear sick at birth as a result of birth trauma, intrauterine insults, chromosomal abnormalities, or other genetic diseases.

2. The nature of the mutation that causes the dysfunction of the gene usually varies from family to family. This results in variation in severity of the phenotype in different families. An exception to this is found when a specific mutation has been preserved in an ethnic group primarily from inbreeding (the founder effect). An example is maple syrup urine disease in Old Order Mennonites in the United States (mainly in Lancaster County, PA), in whom all the affected infants have the same mutation and hence the same phenotype (see Chapter 85.6).

3. Mutations causing severe malfunction of the gene or its product result in clinical manifestations shortly after birth. In general, the earlier the appearance of clinical symptoms, the more severe the disease.

4. The majority of conditions are inherited as autosomal recessive traits. Therefore, a history of consanguinity in the parents or of an unexplained death of a family member in the neonatal period may raise the question of an inherited metabolic disease in the sick infant.

5. Most genetic metabolic conditions can be controlled successfully by some form of therapy, and a few can be potentially cured by the use of bone marrow or liver transplants. These patients can have a normal life if diagnosed and treated early, before irreversible damage to organs, especially to the brain, occurs. This underlines the importance of early diagnosis, which can be achieved through mass screening of all newborn infants.

**MASS SCREENING OF NEWBORN INFANTS**

Common characteristics of genetic metabolic conditions and the significance of early diagnosis make a strong argument for screening all newborn infants for the presence of these conditions. During the past half-century, methods have been developed to screen all infants inexpensively with accurate and fast-yielding results. Tandem mass spectrometry is the latest technical advance in the field. This method requires a few drops of blood to be placed on a filter paper and mailed to a central laboratory for assay. A large number of genetic conditions can be identified by this method when complemented by a few equally efficient assays for other specific disorders (Tables 84-1 and 84-2).

Severe forms of some of these diseases may cause clinical manifestations before the results of the newborn screening become available. It should also be noted that these methods may identify mild forms of inherited metabolic conditions, some of which may never cause clinical manifestations in the lifetime of the individual. Potential psychosocial implications of such findings can be drastic and deserve serious consideration. An example of this is 3-methylcrotonyl-coenzyme A carboxylase deficiency, which has been identified with unexpectedly high frequency in screening programs using tandem mass spectrometry. The majority of these children have remained asymptomatic (see Chapter 85.6).

**CLINICAL MANIFESTATIONS OF GENETIC METABOLIC DISEASES**

Physicians and other healthcare providers who care for children should familiarize themselves with early manifestations of genetic metabolic disorders, because (1) severe forms of some of these conditions may cause symptoms before the results of screening studies become available, and (2) the current screening methods, although quite extensive, identify a small number of all inherited metabolic conditions. In the newborn period, the clinical findings are usually nonspecific and similar to those seen in infants with sepsis. A genetic disorder of metabolism should be considered in the differential diagnosis of a severely ill newborn infant, and special studies should be undertaken if the index of suspicion is high (Fig. 84-1).

Signs and symptoms such as lethargy, poor feeding, convulsions, and vomiting may develop as early as a few hours after birth. Occasionally, vomiting may be severe enough to suggest the diagnosis of pyloric stenosis, which is usually not present, although it may occur simultaneously in such infants. Lethargy, poor feeding, convulsions, and coma may also be seen in infants with hypoglycemia (see Chapters 92 and 107) or hypocalcemia (see Chapters 51 and 571). Measurements of blood concentrations of glucose and calcium and response to intravenous injection of glucose or calcium usually establish these diagnoses. Some of these disorders have a high incidence in specific population groups. Tyrosinemia type 1 is more common among French-Canadians of Quebec than in the general population. Therefore, knowledge of the ethnic background of the patient may be helpful in diagnosis. \textit{Physical examination} usually reveals nonspecific findings; most signs are related to the central nervous system. Hepatomegaly is a common finding in a variety of inborn errors of metabolism. Occasionally, a peculiar odor may offer an invaluable aid to the diagnosis (Table 84-3). A physician caring for a sick infant should smell the patient and the patient’s excreta; for example, patients with maple syrup urine disease have the unmistakable odor of maple syrup in their urine and on their bodies.

Occasionally, the onset of a genetic metabolic condition may occur months or years after birth. These children usually have mutations that render the gene partially nonfunctional. \textit{Clinical manifestations}, such as intellectual disability, motor deficits, developmental regression, convulsions, myopathy, recurrent emesis, and cardiomyopathy, in a child beyond the neonatal period should raise the possibility of an inherited
metabolic disease. There may be an episodic or intermittent pattern, with episodes of acute clinical manifestations separated by periods of seemingly disease-free states. The episodes are usually triggered by stress or a nonspecific catabolic insult such as an infection. The child may die during one of these acute attacks. A genetic disorder of metabolism should be considered in any child with 1 or more of the following manifestations: unexplained intellectual disability, developmental delay or regression, motor deficits or adventitious movements (e.g., dystonia, choreoathetosis), convulsions, unusual odor (particularly during an acute illness); intermittent episodes of unexplained vomiting, acidosis, mental deterioration, psychotic behavior or coma; hepatomegaly; renal stones; muscle weakness; or cardiomyopathy. For example, urea cycle defects may present with confusion, behavioral disturbances, catatonia, hallucinations, psychosis, or depression. Cataract may also be seen in disorders of folate metabolism, porphyria, Wilson disease, and some storage diseases. Severe seizures may be noted in molybdenum cofactor deficiency, biotinidase deficiency, neuronal ceroid lipofuscinos, nonketotic hyperglycinemia, or creatine deficiency.

Diagnosis usually requires a variety of specific laboratory studies. Measurements of serum concentrations of ammonia, bicarbonate, and pH are often very helpful initially in differentiating major causes of genetic metabolic disorders (see Fig. 84-1). Elevation of blood ammonia is usually caused by defects of urea cycle enzymes. Infants with elevated blood ammonia levels from urea cycle defects commonly have normal serum pH and bicarbonate values; without measurement of blood ammonia, they may remain undiagnosed and succumb to their disease. Elevation of serum ammonia is also observed in some infants with certain organic acidemias. These infants are severely acidic because of accumulation of organic acids in body fluids.
Figure 84-1 Initial clinical approach to a full term newborn infant with a suspected genetic metabolic disorder. This schema is a guide to the elucidation of some of the metabolic disorders in newborn infants. Although some exceptions to this schema exist, it is appropriate for most cases.

When blood ammonia, pH, and bicarbonate values are normal, other aminoacidopathies (such as hyperglycinemia) or galactosemia should be considered; galactosemic infants may also manifest cataracts, hepatomegaly, ascites, and jaundice.

**TREATMENT**

The majority of patients with genetic disorders of metabolism respond to 1 or all of the following treatments:

1. Special diets play an important role in the treatment of affected children. Dietary changes should be tailored to the pathophysiology of the condition and vary greatly among disorders.

2. Peritoneal dialysis or hemodialysis for expeditious removal of accumulated noxious compounds. This is a very effective modality for treatment of the acute phase of the condition.

3. Administration of the deficient metabolite.

4. Administration of the cofactor or coenzyme to maximize the residual enzyme activity.

5. Activation of alternate pathways to reduce the noxious compounds accumulated because of the genetic mutation.

6. Administration of the deficient enzyme.


8. Liver transplantation.

The bone marrow and liver transplantation modalities have the potential to cure the metabolic abnormalities. Replacement of the mutant gene with a normal one (gene therapy) is still in the experimental phase.

Treatment of genetic disorders of metabolism is complex and requires medical and technical expertise. The therapeutic regimen often needs to be tailored to the individual patient because of large phenotypic variations in the severity of the disease, even within a single family. Providing education and support for the family is the key to successful long-term therapy. Even in patients with hopeless prognoses every effort should be made to establish correct diagnoses premortem as the autopsy results are often noncontributory to the diagnosis. Effective treatment is best achieved by a team of specialists (physician metabolic genetics specialist, nutritionist, geneticist, neurologist, and psychologist) in a major medical center.

_Bibliography is available at Expert Consult._
Bibliography
Phenylalanine is an essential amino acid. Dietary phenylalanine not utilized for protein synthesis is normally degraded by way of the tyrosine pathway (Fig. 85-1). Deficiency of the enzyme phenylalanine hydroxylase (PAH) or of its cofactor tetrahydrobiopterin (BH₄) causes accumulation of phenylalanine in body fluids and in the brain.

Hyperphenylalaninemia depends on the degree of enzyme deficiency and may vary from very high plasma concentrations (>20 mg/dL or >1,200 µmole/L, classic phenylketonuria) to mildly elevated levels (2-10 mg/dL or 120-600 µmole/L, mild hyperphenylalaninemia). In affected infants with plasma concentrations >20 mg/dL, excess phenylalanine is metabolized to phenylketones (phenylpyruvate and phenylacetate; see Fig. 85-1) that are excreted in the urine, giving rise to the term phenylketonuria (PKU). These metabolites have no role in pathogenesis of central nervous system (CNS) damage in patients with PKU; their presence in the body fluids simply signifies the severity of the condition. The term hyperphenylalaninemia implies lower plasma levels (<20 mg/dL) of phenylalanine. The brain is the main organ affected by hyperphenylalaninemia. The CNS damage in affected patients is caused by the elevated concentration of phenylalanine in brain tissue. The high blood levels of phenylalanine in PKU saturate the transport system across the blood–brain barrier causing inhibition of the cerebral uptake of other large neutral amino acids such as tyrosine and tryptophan. The exact mechanism of damage caused by elevated levels of intracerebral phenylalanine remains elusive. There have been a few adults with classic PKU and normal intelligence who have
never been treated with a phenylalanine-restricted diet. Phenylalanine content of the brain in these individuals was found to be close to that of normal subjects when studied by magnetic resonance spectroscopy (MRS).

**CLASSIC PHENYLKETONURIA**

Severe hyperphenylalaninemia (plasma phenylalanine levels >20 mg/dL), if untreated, invariably results in the development of signs and symptoms of classic PKU, except in rare unpredictable cases (see above).

**Clinical Manifestations**

The affected infant is normal at birth. Profound intellectual disability develops gradually if the infant remains untreated. Cognitive delay may not be evident for the first few months. In untreated patients, 50-70% will have an IQ below 35, and 88-90% will have an IQ below 65. Only 2-5% of untreated patients will have normal intelligence. Many patients require institutional care if the condition remains untreated. Vomiting, sometimes severe enough to be misdiagnosed as pyloric stenosis, may be an early symptom. Older untreated children become hyperactive with autistic behaviors, including purposeless hand movements, rhythmic rocking, and athetosis.

The infants are lighter in their complexion than unaffected siblings. Some may have a seborrheic or eczematoid rash, which is usually mild and disappears as the child grows older. These children have an unpleasant odor of phenylacetic acid, which has been described as musty or mousey. Neurologic signs include seizures (approximately 25%), spasticity, hyperreflexia, and tremors; more than 50% have electroencephalographic abnormalities. Microcephaly, prominent maxillae and sometimes flat or high arched palate, widely spaced teeth, enamel hypoplasia, and growth retardation may be other common findings in untreated children. The clinical manifestations of classic PKU are rarely seen in those countries in which neonatal screening programs for the detection of PKU are in effect.

**Nonphenylketonuria Hyperphenylalaninemas (Milder Forms of Hyperphenylalaninemia)**

In any screening program for PKU, a group of infants is identified in whom initial plasma concentrations of phenylalanine are above normal (i.e., >2 mg/dL or 120 µmole/L) but <20 mg/dL (1,200 µmole/L). These infants do not excrete phenylketones. Patients with non-PKU
Hyperphenylalaninemia may still require dietary therapy, depending on their untreated plasma phenylalanine level. Attempts have been made to classify these patients in different subgroups depending on the degree of hyperphenylalaninemia, but such a practice has little clinical or therapeutic advantage. The possibility of deficiency of BH₄ should be investigated in all infants with the milder forms of hyperphenylalaninemia (see below).

**Diagnosis**

Because of the gradual and nonspecific nature of early clinical symptoms such as vomiting, developmental delay, or eczematoid rash, hyperphenylalaninemia is usually diagnosed through newborn screening in all developed countries. In infants with positive screening results, diagnosis should be confirmed by quantitative measurement of plasma phenylalanine concentration. Identification and measurement of phenylketones in the urine has no place in any screening program. In countries and places where such programs are not in effect, identification of phenylketones in the urine by ferric chloride may offer a simple test for diagnosis of infants with developmental and neurologic abnormalities. Once the diagnosis of hyperphenylalaninemia is established, additional studies for BH₄ metabolism should be performed to rule out BH₄ deficiency as the cause of hyperphenylalaninemia (see below).

**Neonatal Screening for Hyperphenylalaninemia**

Effective and relatively inexpensive methods for mass screening of newborn infants have been developed and are used in the United States and several other countries. A few drops of blood, which are placed on a filter paper and mailed to a central laboratory, are used for assay. The bacterial inhibition assay of Guthrie, which was the first method used for this purpose, has been replaced by more precise and quantitative methods (fluorometric and tandem mass spectrometry). The method of choice is tandem mass spectrometry, which identifies all forms of hyperphenylalaninemia with a low false-positive rate and excellent accuracy and precision. The addition of the phenylalanine:tyrosine molar ratio has further reduced the number of false-positive results. Diagnosis must be confirmed by measurement of plasma phenylalanine concentration. Blood phenylalanine in affected infants with PKU may rise to diagnostic levels as early as 4 hr after birth, even in the absence of protein feeding. It is recommended that the blood for screening be obtained in the first 24-48 hr of life after feeding protein to reduce the possibility of false-negative results, especially in the milder forms of the condition.

**Treatment**

The mainstay of treatment of PKU is a low-phenylalanine diet. The general consensus is to start diet treatment immediately in patients with blood phenylalanine levels above 10 mg/dL (600 µmole/L). Most physicians also advocate phenylalanine-restricted diet in patients with mild hyperphenylalaninemia whose levels are persistently above 6 mg/dL (360 µmole/L). It is generally accepted that infants with persistent (more than a few days) plasma levels of phenylalanine ≥6 mg/dL (360 µmole/L) should be treated with a phenylalanine-restricted diet similar to that for classic PKU. The goal of therapy is to reduce phenylalanine levels in the plasma and brain. Formulas free of or low in phenylalanine are commercially available. The diet should be started as soon as the diagnosis is established. Because phenylalanine is not synthesized endogenously, small amounts of phenylalanine should be added to the diet to prevent phenylalanine deficiency. Dietary deficiency of this amino acid is manifested by lethargy, failure to thrive, anorexia, anemia, rashes, diarrhea, and even death; moreover, tyrosine becomes an essential amino acid in this disorder and its adequate intake must be ensured. Special food items low in phenylalanine are commercially available for dietary treatment of affected children and adults. There is no firm consensus concerning optimal level of blood phenylalanine in affected patients either across different countries or among treatment centers in the United States. In 2001, the National Institutes of Health Consensus Development Panel recommended that plasma phenylalanine levels be maintained between 2 and 6 mg/dL in neonates through 12 yr of age and between 2 and 15 mg/dL in older individuals. Given that brain development continues in adolescence and even in adulthood, maintenance of lower plasma phenylalanine levels (2-10 mg/dL) has been strongly encouraged even after 12 yr of age. The duration of diet therapy is also controversial. Discontinuation of therapy, even in adulthood, may cause deterioration of IQ and cognitive performance. The current recommendation from the 2001 National Institutes of Health Consensus Development Panel is that all patients be kept on a phenylalanine-restricted diet for life. Lifelong adherence to a low phenylalanine diet is extremely difficult. Patients, who maintain good control as children but discontinue the phenylalanine-restricted diet as teenagers or adults, may experience significant difficulties with executive function concentration, emotional liability, and depression. Executive dysfunction may also occur in early treated children in spite of diet treatment.

Given the difficulty of maintaining a strict low-phenylalanine diet, there are continuing attempts to find other modalities for treatment of these patients. Administration of large neutral amino acids (LNAA)s is another approach to diet therapy. LNAA{s (tyrosine, tryptophan, arginine, leucine, isoleucine, valine, methionine, histidine, lysine, threonine, and phenylalanine) share the same transporter protein (LNAA type 1, LAT-1) for transit through the intestinal cell membrane and blood–brain barrier. Binding of LNAA to the transporter protein is a competitive process. The rationale for use of LNAA is that these molecules compete with phenylalanine for transport across the blood–brain barrier; therefore, large concentrations of other LNAA{s in the intestinal lumen and in the blood reduce the uptake of phenylalanine into bloodstream and the brain. Clinical trials to establish the efficacy of this treatment are lacking at this time. Oral administration of BH₄, the cofactor for PAH, may result in reduction of plasma levels of phenylalanine in some patients with PAH deficiency. Plasma levels of phenylalanine in these patients may decrease enough to allow for considerable modification of their dietary restriction. In very rare cases, the diet may be discontinued because the phenylalanine levels remain under 6 mg/dL. The response to BH₄ cannot be predicted consistently on the basis of genotype, especially in compound heterozygous patients. Sapropterin dihydrochloride (Kuvan), a synthetic form of BH₄, which acts as a cofactor in patients with residual PAH activity, is approved by the FDA to reduce phenylalanine levels in PKU. At a dose of 10 mg/kg/day, it reduces phenylalanine levels in up to 40% of patients. Preliminary trials with recombinant phenylalanine ammonia lyase have been encouraging and demonstrated reduced blood levels of phenylalanine during treatment.

Low mineral bone density and osteopenia have been reported in affected individuals of all ages. Although inadequate intake of natural proteins seems to be the major culprit, the exact pathogenesis of this sequela remains unclear.

Long-term care of patients with PKU is best achieved by a team of experienced professionals (metabolic specialist, nutritionist, and psychologist) in a regional treatment center.

**Pregnancy in Women with Hyperphenylalaninemia (Maternal Phenylketonuria)**

Pregnant women with hyperphenylalaninemia who are not on a phenylalanine-restricted diet have a very high risk of having offspring with intellectual disability, microcephaly, growth retardation, congenital malformations, and congenital heart disease. These complications are directly correlated with elevated maternal blood phenylalanine levels during pregnancy. Prospective mothers who have been treated for hyperphenylalaninemia should be maintained on a phenylalanine-restricted diet before and during pregnancy; the best observed outcomes occur when strict control of maternal blood phenylalanine concentration is instituted before pregnancy or by 8 wk of gestation at the latest. The currently recommended phenylalanine concentrations are between 2 and 6 mg/dL (120-360 µmole/L) throughout the pregnancy. All women with hyperphenylalaninemia who are of childbearing age should be counseled properly as to the risk of the just described congenital anomalies in their offspring.
HYPERPHENYLALANINEMIA CAUSED BY DEFICIENCY OF THE COFACTOR TETRAHYDROBIOPTERIN

In 1-3% of infants with hyperphenylalaninemia, the defect resides in 1 of the enzymes necessary for production or recycling of the cofactor BH4 (see Fig. 85-1). If these infants are misdiagnosed as having PKU, they may deteriorate neurologically despite adequate control of plasma phenylalanine. BH4 is synthesized from guanosine triphosphate (GTP) through several enzymatic reactions (see Fig. 85-1). In addition to acting as a cofactor for PAH, BH4 is also a cofactor for tyrosine hydroxylase and tryptophan hydroxylase, which are involved in the biosynthesis of dopamine (Fig. 85-2) and serotonin (see Fig. 85-5), respectively. Therefore, patients with hyperphenylalaninemia as a result of BH4 deficiency also manifest neurologic findings related to deficiencies of the neurotransmitters dopamine and serotonin. Four enzyme deficiencies leading to defective BH4 formation cause hyperphenylalaninemia with concomitant deficiencies of dopamine and serotonin. These include autosomal recessive GTP cyclohydrolase deficiency, pericarbinolamine dehydratase deficiency, dihydropteridine reductase deficiency, and 6-pyruvoyl tetrahydropterin synthase deficiency. More than half of the reported patients have had a deficiency of 6-pyruvoyl tetrahydropterin synthase. Autosomal dominant forms of GTP deficiency and sepiapterin reductase deficiency result in deficiencies of neurotransmitters without hyperphenylalaninemia (see Chapter 85.11 and Fig. 85-1).

Clinical Manifestations

Infants with cofactor deficiency are identified during screening programs for PKU because of evidence of hyperphenylalaninemia. Plasma phenylalanine levels may be as high as those in classic PKU or in the range of milder forms of hyperphenylalaninemia. However, the clinical manifestations of the neurotransmitter disorders differ greatly from those of PKU. Neurologic symptoms of the neurotransmitter disorders often manifest in the first few months of life and include extrapyramidal signs (choreoathetotic or dystonic limb movements, axial and truncal hypotonia, hypokinesia), feeding difficulties, and autonomic abnormalities. Intellectual disability, seizures, hypersalivation, and swallowing difficulties are also seen. The symptoms are usually progressive and often have a marked diurnal fluctuation. Prognosis and outcome strongly depend on the age at which the diagnosis is made and treatment is introduced, but also on the specific nature of the mutation and resulting enzyme defect.

Diagnosis

Despite the low incidence of BH4 defects, all newborns with hyperphenylalaninemia detected through newborn screening should be screened for BH4 defects.

BH4 deficiency and the responsible enzyme defect may be diagnosed by the following studies:

1. Measurement of neopterin (oxidative product of dihydroleopterin triphosphate) and bipterin (oxidative product of dihydropterin and BH4) in body fluids, especially urine (see Fig. 85-1). In patients with GTP cyclohydrolyase deficiency, urinary excretion of both neopterin and bipterin is very low. In patients with 6-pyruvoyl tetrahydropterin synthase deficiency, there is a marked elevation of neopterin excretion and a concomitant decrease in bipterin excretion. In patients with dihydropteridine reductase deficiency, neopterin is normal, but bipterin is very high. Excretion of bipterin increases in this enzyme deficiency because the quinonoid dihydrobipterin cannot be recycled back to BH4. Patients with pericarbinolamine dehydratase deficiency excrete 7-bipterin (an unusual isomer of bipterin) in their urine. In addition, examination of cerebrospinal fluid (CSF) reveals decreased levels of dopamine, serotonin, and their metabolites in all patients with BH4 deficiency (see Chapter 85.11).

2. BH4 loading test. An oral dose of BH4 (20 mg/kg) normalizes plasma phenylalanine and phenylalanine:tyrosine ratio in patients with BH4 deficiency within 4-8 hr. The blood phenylalanine should be elevated (>400 μmol/L) to enable interpretation of the results. This may be achieved by discontinuing diet therapy for 2 days before the test or by administering a loading dose of phenylalanine (100 mg/kg) 3 hr before the test. In BH4-responsive PKU caused by PAH deficiency, blood phenylalanine levels may decrease during the BH4 loading test, but increase later even with BH4 supplementation. Patients who demonstrate phenylalanine levels within normal range over at least a week without a phenylalanine-restricted diet can be continued on BH4 supplementation as the sole treatment for the hyperphenylalaninemia. However, it is imperative that plasma

![Figure 85-2 Other pathways involving tyrosine metabolism. PKU* indicates hyperphenylalaninemia caused by tetrahydrobiopterin (BH4) deficiency (see Fig. 85-1). HVA, homovanillic acid; VMA, vanillylmandelic acid. Enzymes: (1) Tyrosine hydroxylase (TH), (2) aromatic l-amino acid decarboxylase (AADC), (3) dopamine β-hydroxylase (DβH), (4) phenylethanolamine-N-methyltransferase (PNMT), (5) catechol-O-methyltransferase (COMT), (6) monoamine oxidase (MAO).](image-url)
phenylalanine levels are monitored prospectively to ensure that phenylalanine levels remain within the normal range.

3. Enzyme assay. The activity of dihydropteridine reductase can be measured in the dry blood spots on the filter paper used for screening purposes. 6-Pyruvoyltetrahydropterin synthase activity can be measured in the liver, kidneys, and erythrocytes. Carbinolamine dehydratase activity can be measured in the liver and kidneys. GTP cyclohydrolase activity can be measured in the liver and in cytokine (interferon-γ) stimulated mononuclear cells or fibroblasts (the enzyme activity is normally very low in unstimulated cells).

4. Genetic test. Mutation analysis and deletion/duplication studies are clinically available for all these enzyme defects and help to confirm the diagnosis.

Treatment
The goals of therapy are to correct hyperphenylalaninemia and to restore neurotransmitter deficiencies in the CNS. The control of hyperphenylalaninemia is important in patients with cofactor deficiency, because high levels of phenylalanine cause intellectual disability and also interfere with the transport of neurotransmitter precursors (tyrosine, tryptophan) into the brain. Plasma phenylalanine should be maintained as close to normal as possible (<6 mg/dL). This can be achieved by oral supplementation of BH4 (5-20 mg/kg/day). Sapropterin dihydrochloride (Kuvan), a synthetic form of BH4 is commercially available, although it is expensive.

Lifelong supplementation with neurotransmitter precursors such as L-dopa and 5-hydroxytryptophan, along with carbidopa to inhibit degradation of L-dopa before it enters the CNS, is necessary in most of these patients even when treatment with BH4 normalizes plasma levels of phenylalanine. BH4 does not readily enter the brain to restore neurotransmitter production. To minimize untoward side effects (especially L-dopa–induced dyskinesia), the treatment should be started with low doses of L-dopa/carbidopa and 5-hydroxy tryptophan, and should be adjusted based on response to therapy and clinical improvement for each individual patient. Supplementation with folinic acid is also recommended in patients with dihydropteridine reductase deficiency. Unfortunately, attempting to normalize neurotransmitter levels using neurotransmitter precursors usually does not fully resolve the neurologic symptoms as a result of the inability to attain normal levels of BH4 in the brain. Patients often demonstrate intellectual disability, fluctuating abnormalities of tone, eye movement abnormalities, poor balance and coordination, decreased ability to ambulate, and seizures in spite of supplementation with neurotransmitter precursors.

Hyperprolactinemia occurs in patients with BH4 deficiency and may be the result of hypothalamic dopamine deficiency. Measurement of serum prolactin levels may be a convenient method for monitoring adequacy of neurotransmitter replacement in affected patients.

Some drugs, such as trimethoprim sulfamethoxazole, methotrexate, and other antileukemic agents, are known to inhibit dihydropteridine reductase enzyme activity and should be used with great caution in patients with BH4 deficiency.

Genetics and Prevalence
All defects causing hyperphenylalaninemia are inherited as autosomal recessive traits. The prevalence of PKU in the United States is estimated at 1 in 14,000 to 1 in 20,000 live births. The prevalence of non-PKU hyperphenylalaninemia is estimated at 1 in 50,000 live births. The condition is more common in whites and Native Americans and less prevalent in African-Americans, Hispanics, and Asians.

The gene for PAH is located on chromosome 12q23.2 and many disease-causing mutations have been identified in different families. The majority of patients are compound heterozygotes for 2 different mutant alleles. The gene for 6-pyruvoyltetrahydropterin synthase (PTS), the most common cause of BH4 deficiency, resides on chromosome 11q23.1, the gene for dihydropteridine reductase (QDPR) is located on chromosome 4p15.2, and those of carbinolamine dehydratase (PCBD1) and GTP cyclohydrolase (GCH1) are on 10q22.1 and 14q22.2, respectively. Many disease-causing mutations of these genes have been identified. Prenatal diagnosis is possible using specific genetic probes in cells obtained from biopsy of the chorionic villi.

TETRAHYDROBIOPTERIN DEFECTS WITHOUT HYPERPHENYLALANINEMIA
See Chapter 85.11.

Bibliography is available at Expert Consult.

85.2 Tyrosine
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Tyrosine is derived from ingested proteins or is synthesized endogenously from phenylalanine. It is used for protein synthesis and is a precursor of dopamine, norepinephrine, epinephrine, melatonin, and thyroxine. Excess tyrosine is metabolized to carbon dioxide and water (see Fig. 85-1). Hereditary causes of hypertyrosinemia include deficiencies of tyrosine aminotransferase, 4-hydroxyphenylpyruvate dioxygenase (4-HPPD), and fumarylacetoacetate hydratase. Acquired hypertyrosinemia may occur in severe hepatocellular dysfunction (liver failure), scurvy (vitamin C is the cofactor for 4-HPPD), and hyperthyroidism. Hypertyrosinemia is common in blood samples obtained soon after eating and in premature infants.

TYROSINEMIA TYPE I (TYROSINOSIS, HEREDITARY TYROSINEMIA, HEPATORENAL TYROSINEMIA)
This severe disease of the liver, kidney, and peripheral nerves is caused by a deficiency of the enzyme fumarylacetoacetate hydratase. Organ damage is believed to result from accumulation of metabolites of tyrosine degradation, especially fumarylacetocetate and succinylacetone.

Clinical Manifestations and Natural History
Untreated, the affected infant appears normal at birth and typically presents between 2 and 6 mo of age but rarely may become symptomatic in the 1st mo or appear healthy beyond the 1st yr of life. The earlier the presentation, the poorer the prognosis. The 1 yr mortality of untreated children, which is approximately 60% in infants who develop symptoms before 2 mo of age, decreases to 4% in infants who become symptomatic after 6 mo of age.

An acute hepatic crisis commonly heralds the onset of the disease and is usually precipitated by an intercurrent illness that produces a catabolic state. Fever, irritability, vomiting, hemorrhage, hepatomegaly, jaundice, elevated levels of serum transaminases, and hypoglycemia are common. An odor resembling boiled cabbage may be present, resulting from increased methionine metabolites. Most hepatic crises resolve spontaneously, but may progress to liver failure and death. Between the crises, varying degrees of failure to thrive, hepatomegaly, and coagulation abnormalities often persist. Cirrhosis and eventually hepatocellular carcinoma occur with increasing age. Carcinoma is unusual before 2 yr of age.

Episodes of acute peripheral neuropathy resembling acute porphyria occur in approximately 40% of affected children. These crises, often triggered by a minor infection, are characterized by severe pain, often in the legs, associated with extensor hypertonia of the neck and trunk, vomiting, paralytic ileus, and, occasionally, self-induced injuries of the tongue or buccal mucosa. Marked weakness and paralysis occur in about 30% of episodes, which may lead to respiratory failure requiring mechanical ventilation. Crises typically last 1-7 days but recovopa from paralytic crises can require weeks to months.

Renal involvement is manifested as a Fanconi-like syndrome with hyperphosphaturia, hypophosphatemia, normal anion gap metabolic acidosis, and vitamin D–resistant rickets. Nephromegaly and nephrocalcinosis may be present on ultrasound examination. Glomerular failure may occur in adolescents and older patients.
Bibliography


Hypertrophic cardiomyopathy and hyperinsulinism are seen in some infants.

**Laboratory Findings**

The presence of elevated levels of succinylacetone in serum and urine is diagnostic for tyrosinemia type I (see Fig. 85-1). In untreated patients, the blood level of α-fetoprotein is increased, often markedly, and liver-synthesized coagulation factors are decreased in most patients; serum levels of transaminases are often increased, with marked increases being possible during acute hepatic episodes. Serum concentration of bilirubin is usually normal but can be increased with liver failure. Increased levels of α-fetoprotein are present in the cord blood of affected infants, indicating intrauterine liver damage. Plasma tyrosine levels are usually elevated at diagnosis but this is a nonspecific finding and is dependent on dietary intake. Plasma levels of other amino acids, particularly methionine, may also be elevated in patients with liver damage. Hyperphosphaturia, hypophosphatemia, and generalized aminoaciduria may occur. The urinary level of 5-aminolevulinic acid is elevated because of inhibition of 5-aminolevulinic hydratase by succinylacetone.

**Diagnosis** is usually established by demonstration of elevated levels of succinylacetone in urine or blood. Neonatal screening for hyper-tyrosinemia detects only a minority of patients with tyrosinemia type I. Succinylacetone, which is now assayed by some neonatal screening programs, has higher sensitivity and specificity than tyrosine and is the preferred metabolite for screening. Tyrosinemia type I should be differentiated from other causes of hepatitis and hepatic failure in infants, including galactosemia, hereditary fructose intolerance, neonatal iron storage disease, giant cell hepatitis, and citrullinemia type II (see Chapter 85.12).

**Treatment and Outcome**

A diet low in phenylalanine and tyrosine can slow but does not halt the progression of the condition. The treatment of choice is nitisinone, which inhibits tyrosine degradation at 4-HPPD (see Fig. 85-1). This treatment prevents acute hepatic and neurologic crises. Although nitisinone stops or greatly slows disease progression, some pretreatment liver damage is not reversible. Therefore, patients must be followed for development of cirrhosis or hepatocellular carcinoma. On imaging, the presence of even a single liver nodule usually indicates underlying cirrhosis. Most liver nodules in tyrosinemic patients are benign but current imaging techniques do not accurately distinguish all malignant nodules. Liver transplantation is an effective therapy for tyrosinemia type I and alleviates the risk of hepatocellular carcinoma. The impact of nitisinone treatment on the need for liver transplantation is still under study but the greatest effect is in patients treated early, such as children detected by neonatal screening, prior to the development of clinical symptoms. In early-treated patients, nitisinone has greatly reduced the need for liver transplantation. At any age, nitisinone treatment eliminates the occurrence of acute episodes of liver failure and neurologic crises although they are at risk for impaired cognitive function. Because nitisinone treatment causes an increase in plasma tyrosine level, a diet restricted in tyrosine and phenylalanine is prescribed. Rarely, nitisinone-treated patients develop corneal crystals, presumably of tyrosine, which are reversible by strict dietary compliance. This finding, combined with observations of developmental delay in some patients with tyrosinemia type II who chronically have elevated tyrosine levels, suggest that a diet low in phenylalanine and tyrosine should be continued in patients treated with nitisinone. The dietary treatment of patients with tyrosine and phenylalanine restriction necessitates surveillance to ensure adequate intakes of other nutrients and amino acids.

**Genetics and Prevalence**

Tyrosinemia type I is inherited as an autosomal recessive trait. The gene for fumarylacetoacetate hydrolase (FAH) maps to chromosome 15q 25.1 and; numerous disease-causing mutations of the gene have been reported. DNA analysis is useful for molecular prenatal diagnosis if the familial mutations are known and for carrier testing in groups at risk for specific mutations such as French-Canadians from the Saguenay-Lac Saint-Jean region of Quebec. The prevalence of the condition is estimated to be 1 in 1,846 live births in the Saguenay-Lac Saint-Jean region and approximately 1 in 100,000 live births worldwide. But tyrosinemia type I is panethnic; lack of French-Canadian or Scandinavian ancestry does not exclude the diagnosis. Prenatal diagnosis is typically performed by measurement of succinylacetone in amniotic fluid, or if the familial mutations are known, by DNA analysis of amniocytes or of chorionic villi.

**TYROSINEMIA TYPE II (RICHNER-HANHART SYNDROME, OCULOCUTANEOUS TYROSINEMIA)**

This rare autosomal recessive disorder is caused by deficiency of tyrosine aminotransferase and results in palp and plantar hyperkeratosis, herpetiform corneal ulcers, and intellectual disability (see Fig. 85-1). **Ocular manifestations**, which may occur as early as 6 mo of age, include excessive tearing, redness, pain, and photophobia. Corneal lesions are presumed to be because of tyrosine deposition. In contrast to herpetic ulcers, corneal lesions in tyrosinemia type II stain poorly with fluorescein and often are bilateral. **Skin lesions**, which may develop later in life, include painful, nonpruritic hyperkeratotic plaques on the soles, palms, and fingertips. Intellectual disability, which occurs in approximately 50% of patients, is usually mild to moderate.

The principal laboratory finding in untreated patients is marked hypertyrosinemia (20-50 mg/dL; 1,100-2,750 μmol/L). Surprisingly, 4-hydroxyphenylpyruvic acid and its metabolites are also elevated in urine despite being downstream from the metabolic block (see Fig. 85-1). This is hypothesized to occur via the action of other transaminases in the presence of high tyrosine concentrations, producing 4-hydroxyphenylpyruvic acid in cellular compartments like the mitochondrion in which it cannot be further degraded. In contrast to tyrosinemia type I, liver and kidney function are normal, as are serum concentrations of other amino acids and succinylacetone. Tyrosinemia type II is caused by TAT gene mutations, causing deficiency of cytosolic tyrosine aminotransferase activity in liver.

**Diagnosis** of type II tyrosinemia is established by assay of plasma tyrosine concentration in patients with suggestive findings. Molecular diagnosis is possible. Assay of liver tyrosine aminotransferase activity requires a liver biopsy and is rarely indicated.

**Treatment** with a diet low in tyrosine and phenylalanine improves the biochemical abnormalities and can normalize the skin and eye. The claim that intellectual disability may be prevented by early diet therapy is reasonable and is consistent with some case reports. The gene for tyrosine aminotransferase (TAT) maps to chromosome 16q22.2 and several disease-causing mutations have been identified. About half of reported cases are of Italian descent.

**TYROSINEMIA TYPE III (PRIMARY DEFICIENCY OF 4-HYDROXYPHENYLPYRUVATE DIOXYGENASE [4-HPPD])**

Only a few cases have been reported; most were detected by amino acid chromatography performed for various neurologic findings. Age at presentation has been from 1-17 mo. Developmental delay, seizures, intermittent ataxia, and self-destructive behavior are reported; a causal link to 4-HPPD deficiency is not formally established. Liver and renal abnormalities are absent. Asymptomatic infants with 4-HPPD deficiency have been identified by neonatal screening for hypertyrosinemia.

The **diagnosis** is suspected in children with sustained moderate increases in plasma levels of tyrosine (typically 350-700 μmol/L on a normal diet) and the presence of 4-hydroxyphenylpyruvic acid and its metabolites in urine. Diagnosis may be refined by demonstrating the presence of mutations in the gene (HPD) for 4-HPPD on chromosome 12q42.31, or rarely, by demonstrating a low activity of 4-HPPD enzyme; the latter requires a liver biopsy and is not usually indicated.

Given the possible association with neurologic abnormalities, dietary reduction of plasma tyrosine levels is prudent. It is also logical...
to attempt a trial of vitamin C, the cofactor for 4-HPPD. The condition is inherited as an autosomal recessive trait.

**HAWKINSINURIA**

Certain missense mutations in the gene for 4-HPPD result in an abnormal enzyme activity. The mutant enzyme, incapable of normally oxidizing 4-hydroxyphenylpyruvate to homogentisic acid, forms an intermediate that reacts with cysteine to form the unusual organic acid hawkinsin ((2-L-cysteinyl-5-S-y1-1,4-dihydroxy-cyclohex-5-en-1-y1)acetic acid, named after the first affected family, Fig. 85.1); secondary glutathione deficiency may occur. Hawkinsinuria is inherited as an autosomal dominant trait and a few specific causative missense mutations have been identified. The same mutation, a substitution of threonine for the normal alanine codon at position 33 of the 4-HPPD gene, has been identified in unrelated patients with hawkinsinuria. The condition is, perhaps, more prevalent than once realized.

Individuals with this disorder are symptomatic only during infancy. The symptoms usually appear in the first few months of life; commonly after weaning from breastfeeding and with the introduction of a high-protein diet. Severe metabolic acidosis, ketosis, failure to thrive, mild hepatomegaly, and an unusual odor (described as like that of a swimming pool) are reported manifestations of this disorder. Mental development is usually normal.

Symptomatic infants and asymptomatic affected children and adults excrete hawkinsin, 4-hydroxyphenylpyruvic acid, and its metabolites (4-hydroxyphenyllactic and 4-hydroxyphenylacetic acids), 4-hydroxycyclohexyacetic acid and 5-oxoproline (owing to secondary glutathione deficiency) in their urine. The plasma tyrosine level, which is moderately elevated in the symptomatic infants, may become normal in the asymptomatic affected individuals. Treatment consists of a low-protein diet during infancy. Breastfeeding is encouraged. A trial with large doses of vitamin C (up to 1,000 mg/24 hr) is also recommended. The mutant enzyme is susceptible to inhibition by nitisinone; clinical studies showing the efficacy of this agent in symptomatic infants are lacking at this time, and the indications for its use are not known.

**TRANSIENT TYROSINEMIA OF THE NEWBORN**

In a small number of newborn infants, plasma tyrosine may be as high as 60 mg/dL (3,300 µmole/L) during the 1st 2 wk of life. Most affected infants are premature and are receiving high-protein diets. Transient tyrosinemia is felt to result from delayed maturation of 4-HPPD (see Fig. 85-1). Lethargy, poor feeding, and decreased motor activity are noted in some patients. Most are asymptomatic and are identified by a high blood phenylalanine or tyrosine level on routine screening. Laboratory findings include marked elevation of plasma tyrosine with a moderate increase in plasma phenylalanine. The finding of hypertyrosinemia differentiates this condition from PKU. 4-Hydroxyphenylpyruvic acid and its metabolites (see above) are present in the urine. Hypertyrosinemia usually resolves spontaneously in the 1st mo of life. It can be corrected promptly by reducing dietary protein to below 2 g/kg/24 hr and by administering vitamin C (200-400 mg/24 hr). Mild intellectual deficits have been reported in some infants who had this condition, but the causal relationship to hypertyrosinemia is not conclusively established.

**ALKAPTONURIA**

This rare (with an incidence of approximately 1 in 250,000 live births) autosomal recessive disorder is caused by a deficiency of homogentisic acid oxidase (homogentisate 1,2-dioxigenase). In alkaptonuria, large amounts of homogentisic acid are formed (see Fig. 85-1); secondary glutathione deficiency may occur. Alkaptonuria is inherited as an autosomal dominant trait and a few specific causative missense mutations have been identified. The same mutation, a substitution of threonine for the normal alanine codon at position 33 of the 4-HPPD gene, has been identified in unrelated patients with hawkinsinuria. The condition is, perhaps, more prevalent than once realized.

The main clinical manifestations of alkaptonuria consist of ochronosis and arthritis in adulthood. The only sign in children is a blackening of the urine on standing, caused by oxidation and polymerization of homogentisic acid. A history of gray- or black-stained diapers should suggest the diagnosis. This sign may never be noted; hence, diagnosis is often delayed until adulthood. Ochronosis, which is seen clinically as dark spots on the sclera or cartilage, results from the accumulation of the black polymer of homogentisic acid. Arthritis is another result of this deposition and can be disabling with advancing age. It involves the large joints (spine, hip, and knee) and is usually more severe in males. Like rheumatoid arthritis, the alkaptonuric arthritis has acute exacerbations, but the radiologic findings are typical of osteoarthritis, with characteristic narrowing of the joint spaces and calcification of the intervertebral discs. High incidence of heart disease (mitral and aortic valvulitis, calcification of the heart valves, and myocardial infarction) has been noted.

The *diagnosis* is confirmed by finding massive excretion of homogentisic acid on urine organic acid testing. Tyrosine levels are normal. The enzyme is expressed only in the liver and kidneys.

**Treatment** of the arthritis is symptomatic. Nitisinone efficiently reduces homogentisic acid production in alkaptonuria. If presymptomatic individuals are detected, treatment with nitisinone, combined with a phenylalanine- and tyrosine-restricted diet, seems reasonable, although no experience is available regarding long-term efficacy.

The gene for homogentisic acid oxidase (HGD) maps to chromosome 3q13.3. Several disease-causing mutations have been identified. Alkaptonuria is commonest in the Dominican Republic and Slovakia.

**TYROSINE HYDROXYLASE DEFICIENCY**

See Chapter 85.11.

**ALBINISM** (See also Chapters 622 and 653)

Albinism is caused by deficiency of melanin, the main pigment of the skin and eye (Table 85-1). Melanin is synthesized by melanocytes from tyrosine in a membrane-bound intracellular organelle, the melanosome. Melanocytes originate from the embryonic neural crest and migrate to the skin, eyes (choroid and iris), hair follicles, and inner ear. The melanin in the eye is confined to the iris stromal and retinal pigment epithelia, whereas in skin and hair follicles, it is secreted into the epidermis and hair shaft. Albinism can be caused by deficiencies of melanin synthesis, by some hereditary defects of melanosomes, or by disorders of melanocyte migration. Neither the biosynthetic pathway of melanin nor many facets of melanocyte cell biology are completely elucidated (see Fig. 85-2). The end products are 2 pigments: *pheomelanin*, which is a yellow-red pigment, and *eumelanin*, a brown-black pigment.

| Table 85-1 Classification of Major Causes of Albinism |
|-----------------|--------|-----------------|
| **TYPE**        | **GENE** | **CHROMOSOME**  |
| Oculocutaneous Albinism (OCA) |       |                 |
| OCA1 (tyrosinase deficient) | TYR    | 11q14-q21       |
| OCA1A (severe deficiency)   | TYR    | 11q14-q21       |
| OCA1B (mild deficiency)*    | TYR    | 11q14-q21       |
| OCA2 (tyrosinase positive)  | OCA2   | 15q12-q13       |
| OCA3 (Rufous, red OCA)      | TYRP1† | 9p23            |
| OCA4                        | SLC45A2| 5p13.3          |
| Hermansky-Pudlak syndrome   | HP51-9 | Different       |
| Chédiak-Higashi syndrome    | LYST   | 1q42.1          |
| Ocular Albinism (OA)         | OA     | Xp22.3          |
| OA1 (Nettleship-Falls type)  |        |                 |
| Localized Albinism           | KIT    | 4q12            |
| Piebaldism                   |        |                 |
| Waardenburg syndrome (WS1-WS4) | See text |                 |

*This includes Amish, minimal pigment, yellow albinism, and platinum and temperature-sensitive variants.

†Includes brown OCA.

‡Tyrosinase-related protein 1.
Clinically, primary albinism can be generalized or localized. Primary generalized albinism can be either ocular or oculocutaneous. Some syndromes feature albinism in association with platelet, immunological, or neurological dysfunction.

In generalized oculocutaneous albinism, hypopigmentation can be either complete or partial. Individuals with complete albinism do not develop either generalized (tanning) or localized (pigmented nevi) skin pigmentation.

The diagnosis of albinism is usually evident, but for some white children whose families are particularly light-skinned, normal variation may be a diagnostic consideration. Unlike patients with albinism, normal fair-skinned children progressively develop pigmentation with age, do not exhibit the eye manifestations of albinism, and have pigmentary development similar to other family members. The clinical diagnosis of oculocutaneous albinism, as opposed to other types of cutaneous hypopigmentation, requires the presence of characteristic eye findings.

The ocular manifestations of albinism include hypopigmentation of iris and retina with foveal hypoplasia along with, reduced visual acuity, refractive errors, nystagmus, alternating strabismus, and a red reflex (diffuse reddish hue of the iris produced during ophthalmoscopic or slit-lamp examination of the eye). There is also an abnormality in routing of the optic fibers at the chiasm. Unlike normally in pigmented individuals, in patients with albinism the majority of the nerve fibers from the temporal side of the retina cross to the contralateral hemisphere of the brain. This results in lack of biocular (stereoscopic) vision and depth perception, and in repeated switching of vision from eye to eye, causing alternating strabismus. This abnormality also causes a characteristic pattern of visual-evoked potentials. These findings are highly specific for albinism and can be used to formally establish the clinical diagnosis. Regular ophthalmologic follow-up is recommended for patients with oculocutaneous albinism; correction of refractive errors can maximize visual function. Normally the alternating strabismus does not result in amblyopia and does not require surgery.

Patients with albinism should be counseled to avoid UV radiation by wearing protective long-sleeved clothing and by using sunscreens with a sun protection factor rating above 30. All forms of oculocutaneous albinism are autosomal recessive traits.

Melanin is also present in the cochlea. Albino individuals may be more susceptible to ototoxic agents such as gentamicin.

Many clinical forms of albinism have been identified. Some of the seemingly distinct clinical forms are caused by different mutations of the same gene. Several genes located on different chromosomes are involved in melanogenesis (see Table 85-1). Attempts to differentiate types of albinism based on the mode of inheritance, tyrosinase activity, or the extent of hypopigmentation have failed to yield a comprehensive classification. The following classification is based on the distribution of albinism in the body and the type of mutated gene.

Mutation detection is clinically available for most albinism genes (see Table 85-1). Molecular diagnosis is of little use therapeutically in isolated albinism but can be helpful for precise genetic counseling of families.

**Oculocutaneous (Generalized) Albinism**

Lack of pigment is generalized, affecting skin, hair, and eyes. At least 4 genetically distinct forms of oculocutaneous albinism (OCA) have been identified: OCA1, OCA2, OCA3, and OCA4. The lack of pigment is complete in patients with OCA1 A; the other types may not be clinically distinguishable from one another. All affected individuals have oculocutaneous manifestations of albinism (see above). All forms are inherited as autosomal recessive traits.

**OCA1 (Tyrosinase-Deficient Albinism)**

The defect in these patients resides in the tyrosinase gene, **TYR**, located on chromosome 11q14.3. Many mutant alleles have been identified. Most affected individuals are genetic compounds, heterozygous for 2 different mutant alleles. A clinical clue to the diagnosis of OCA1 is complete lack of pigment at birth. The condition can be subdivided to OCA1 A and OCA1 B, based on enzyme activity and difference in clinical manifestations as a function of age.

**OCA1 A (Tyrosinase-Negative OCA)**

In these individuals, who have the most severe form of OCA, both **TYR** alleles have mutations that completely inactivate tyrosinase. Clinically, lack of pigment in the skin (milky white), hair (white hair), and eyes (red gray irides) is evident at birth and remains unchanged throughout life. They do not tan and do not develop pigmented nevi or freckles.

**OCA1 B**

These patients have **TYR** gene mutations that preserve some residual activity. Clinically they completely lack pigment at birth, but with age become light blond with light blue or hazel eyes. They develop pigmented nevi and freckles and they may tan. OCA1 B patients, depending on the degree of pigmentation, were once subdivided into different groups and thought to be genetically distinct.

**OCA2 (Tyrosinase-Positive OCA)**

This is the most common form of generalized OCA, particularly in African blacks. Clinically, the phenotype is highly variable; most patients demonstrate some pigmentation of the skin and eyes at birth and continue to accumulate pigment throughout their lives. The hair is yellow at birth and may darken with age. They have pigmented nevi and freckles and some may tan. They may be clinically indistinguishable from OCA1 B. Individuals with OCA2 however, have normal tyrosinase activity in hair bulbs. The defect is in the OCA2 gene which is homologous to the p (pink-eyed dilution) gene in the mouse. This gene produces the P protein, a melanosomal membrane protein. Patients with forms of Prader-Willi and Angelman syndromes caused by microdeletion of chromosome 15q12 that includes the OCA2 gene have mild pigmentary deficiency (see Chapter 81.8).

**OCA3 (Rufous Albinism)**

This form has been identified only in Africans, African-Americans, and natives of New Guinea. Patients have reddish hair and reddish brown skin as adults. The skin color is peculiar to this form. In the young, the coloration may resemble that of OCA1. Patients with OCA3 can make pheomelanin but not eumelanin. The mutation is in the tyrosinase-related protein 1 (**TYRP1**) gene (located on chromosome 9p23), the function of which is not well-understood.

**OCA4**

Similar manifestations to OCA3 (both in the skin and the eyes) have been observed in patients (mostly from Japan) with mutations in the **SLC45A2** (previously called **MATP**) gene located on chromosome 5p13.2.

**Ocular Albinism**

Ocular albinism (OA) is limited to the eye. All the eye findings of albinism (see above) are present. Most cases are X-linked (OA1).

**Ocular Albinism 1 (Nettleship-Falls Type)**

Only the hemizygous male has the complete manifestation. Segments of abnormal retinal pigmentation may be present in heterozygous females. An X-linked OA with late-onset sensorineural deafness has also been reported. The diagnosis of ocular albinism 1 (OA1) is evident in males with the features of albinism in the eye, normal skin pigmentation, and a positive family history suggestive of an X-linked recessive transmission. Mild hypopigmentation of the skin (compared to unaffected siblings) may be present. It is a nonprogressive disorder and the eye findings, in fact, often improve with age. In patients who are the first of their families to be affected, electron microscopic demonstration of characteristic mega melanosomes in skin biopsies or hair root specimens is useful, as is mutation analysis of the OA1 gene on chromosome Xp22.2.
Syndromic Forms of Generalized Albinism

Hermansky-Pudlak Syndrome
This group of autosomal recessive disorders is caused by mutations in 1 of 9 different genes located on different chromosomes, HPS1 to HPS9. Hermansky-Pudlak syndrome is suspected in patients with albinism and a bleeding diathesis. Disease subtype can be established with molecular studies.

The HPS genes are necessary for normal structure and function of lysosome-derived organelles, including melanosomes and platelet dense bodies. Patients have a tyrosinase-positive OCA of variable severity associated with platelet dysfunction (owing to the absence of platelet dense bodies). A ceroid-like material accumulates in tissues. Hermansky-Pudlak syndrome is most prevalent in 2 regions of Puerto Rico (type 1 in the northwest and type 3 in the central regions as a result of different founder effects). The cutaneous and ocular symptoms of albinism are present. Patients can develop epistaxis, postsurgical bleeding, or abundant menses. Bleeding time is prolonged but no other symptoms of albinism are present. The diagnosis is usually made after 3 yr of age, when subluxation of the ocular lens (ectopia lentis) occurs. This causes severe myopia and iridodonesis (quivering of the iris). Astigmatism, glaucoma, staphyloma, cataracts, retinal detachment, and optic atrophy may develop later in life. Progressive intellectual disability is common. Normal intelligence has been reported. In an international survey of more than 600 patients, IQ scores ranged from 10–135. Higher IQ scores are seen in vitamin B6–responsive patients. This condition is caused by a homozygous mutation in the PAX3 gene. Type 4 (WS4), associated with Hirschsprung disease, is heterogeneous; mutations in different genes (EDN3, EDNRB, or SOX10) have been identified in different patients.

Other causes of localized hypopigmentation are discussed in other chapters (e.g., hypomelanosis of Ito, see Chapters 81 and 653; and vitiligo, see Chapter 655).

Bibliography is available at Expert Consult.

85.3 Methionine

Iraj Rezvani and David S. Rosenblatt

The usual pathway for catabolism of methionine, an essential amino acid, produces S-adenosylmethionine, which serves as a methyl group donor for methylation of a variety of compounds in the body, and cysteine, which is formed through a series of reactions collectively called trans-sulfuration (Fig. 85-3).

HOMOCYSTINURIA (HOMOCYSTINEMIA)

Normally, most homocysteine, an intermediate compound of methionine degradation, is remethylated to methione. This methionine-sparing reaction is catalyzed by the enzyme methionine synthase, which requires a metabolite of folate acid (5-methyltetrahydrofolate) as a methyl donor and a metabolite of vitamin B12 (methylcobalamin), as well as S-adenosylcobalamin, as cofactors (see Fig. 85-3). Only approximately 20% of total homocysteine (and its dimer homocystine) is in free form in the plasma of normal individuals. The rest is bound to proteins as mixed disulfides. Three major forms of homocystinemia and homocystinuria have been identified.

Homocystinuria Caused by Cystathionine β-Synthase Deficiency (Classic Homocystinuria)

This is the most common inborn error of methionine metabolism. Approximately 40% of affected patients respond to high doses of vitamin B6 and usually have milder clinical manifestations than those who are unresponsive to vitamin B6 therapy. These patients possess some residual enzyme activity. Infants with this disorder are normal at birth. Clinical manifestations during infancy are nonspecific and may include failure to thrive and developmental delay. The diagnosis is usually made after 3 yr of age, when subluxation of the ocular lens (ectopia lentis) occurs. This causes severe myopia and iridodonesis (quivering of the iris). Astigmatism, glaucoma, staphyloma, cataracts, retinal detachment, and optic atrophy may develop later in life. Progressive intellectual disability is common. Normal intelligence has been reported. In an international survey of more than 600 patients, IQ scores ranged from 10–135. Higher IQ scores are seen in vitamin B6–responsive patients. Psychiatric and behavioral disorders have been observed in more than 50% of affected patients. Convulsions occur in approximately 20% of patients. Affected individuals with homocystinuria manifest skeletal abnormalities resembling those of Marfan syndrome (see Chapter 702); they are usually tall and thin, with elongated limbs and arachnodactyly. Scoliosis, pectus excavatum or carinatum, genu valgum, pes cavus, high-arched palate, and crowding of the teeth are commonly seen. These children usually have fair complexions, blue eyes, and a peculiar malar flush. Generalized osteoporosis, especially of the spine, is the main roentgenographic finding. Thromboembolic episodes involving both large and small vessels, especially those of the brain, are common and may occur at any age. Optic atrophy, paralysis, cor pulmonale, and severe hypertension (from renal infarcts) are among the serious consequences of thromboembolism, which is caused by...
Bibliography


changes in the vascular walls and increased platelet adhesiveness secondary to elevated homocysteine levels. The risk of thromboembolism increases after surgical procedures. Spontaneous pneumothorax and acute pancreatitis are rare complications.

Elevations of both methionine and homocysteine (or homocystine) in body fluids are the diagnostic laboratory findings. Freshly voided urine should be tested for homocystine because this compound is unstable and may disappear as the urine is stored. Cystine is low or absent in plasma. The diagnosis may be established by assay of the enzyme in liver biopsy specimens, cultured fibroblasts, or phytohemagglutinin-stimulated lymphocytes or by DNA analysis.

Treatment with high doses of vitamin B₆ (200-1,000 mg/24 hr) causes dramatic improvement in most patients who are responsive to this therapy. The degree of response to vitamin B₆ treatment may be different in different families. Some patients may not respond because of folate depletion; a patient should not be considered unresponsive to vitamin B₆ until folic acid (1-5 mg/24 hr) has been added to the treatment regimen. Restriction of methionine intake in conjunction with cysteine supplementation is recommended for patients who are unresponsive to vitamin B₆. The need for dietary restriction and its extent remains controversial in patients with vitamin B₆-responsive form. In some patients with this form, addition of betaine may obviate the need for any dietary restriction. Betaine (trimethylglycine, 6-9 g/24 hr for adults or 200-250 mg/kg/day for children) lowers homocysteine levels in body fluids by remethylating homocysteine to methionine (see Fig. 85-3); this may result in further elevation of plasma methionine levels. This treatment has produced clinical improvement (preventing vascular events) in patients who are unresponsive to vitamin B₆ therapy. Cerebral edema has occurred in a patient with vitamin B₆-nonresponsive homocystinuria and dietary noncompliance during betaine therapy. Administration of large doses of vitamin C (1 g/day) has improved endothelial function; long-term clinical efficacy is not known.

More than 100 pregnancies in women with the classic form of homocystinuria have been reported with favorable outcomes for both mothers and infants. The majority of infants were full-term and normal. Postpartum thromboembolic events occurred in a few mothers. All but 1 of the 38 affected male patients has had normal offspring.

The screening of newborn infants for classic homocystinuria has been performed worldwide and a prevalence of 1 in 200,000 to 1 in 350,000 live births has been estimated. The condition seems more common in New South Wales, Australia (1 in 60,000 live births), and Ireland. Early treatment of patients identified by the screening process has produced favorable results. The mean IQ of 16 patients with vitamin B₆-unresponsive form treated in early infancy was 94 ± 4. Dislocation of the lens seemed to be prevented in some patients.

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**Figure 85-3** Pathways in the metabolism of sulfur-containing amino acids. Enzymes: (1) Methionine adenosyltransferase (MAT I/III), (2) glycine-N-methyltransferase, (3) adenosylhomocysteine hydrolase, (4) cystathionine synthase, (5) cystathionase, (6) sulfite oxidase, (7) betaine homocysteine methyltransferase, (8) methylene tetrahydrofolate reductase, (9) Methionine synthase (cblG).
Homocystinuria is inherited as an autosomal recessive trait. The gene for cystathionine β-synthase (CBS) is located on chromosome 21q22.3. Prenatal diagnosis is feasible by performing an enzyme assay of cultured amniotic cells or chorionic villi or by DNA analysis. Many disease-causing mutations (>150) have been identified in different families. The majority of affected patients are compound heterozygotes for 2 different alleles. Heterozygous carriers are usually asymptomatic; thromboembolic events and coronary heart disease are more common in these individuals than in the normal population.

**Homocystinuria Caused by Defects in Methylcobalamin Formation**

Methylcobalamin is the cofactor for the enzyme methionine synthase, which catalyzes remethylation of homocysteine to methionine. There are at least 7 distinct defects in the intracellular metabolism of cobalamin that may interfere with the formation of methylcobalamin. To better understand the metabolism of cobalamin, see methylmalonic acidemia (Fig. 85-4; see Chapter 85.6 and Fig. 85-3). The 7 defects are designated as cblC, cblD (including cblD variant 1), cblE (methionine synthase reductase), cblG (methionine synthase), and cblF, cblI, and cblX. Patients with cblI, cblD (not including those with cblD variant 1 or variant 2), cblE, cblF, and cblI X defects have methylmalonic acidemia in addition to homocystinuria, because formation of both adenosylcobalamin and methylcobalamin is impaired (See Chapter 85.6 for further information about these defects.).

Patients with cblI, cblG, and cblD variant 1 defects are unable to form methylcobalamin and develop homocystinuria without methylmalonic acidemia (see Fig. 85-4); fewer than 40 patients are known with each of these diseases.

The clinical manifestations are similar in patients with all of these defects. Vomiting, poor feeding, failure to thrive, hypotonia, seizures, and developmental delay may occur in the first few months of life. One patient with the cblG defect was not symptomatic (except for mild developmental delay) until she was 21 yr old when she developed difficulty in walking and numbness of the hands. Laboratory findings include megaloblastic anemia, homocystinuria, and hypermethioninemia. The presence of megaloblastic anemia differentiates these defects from homocystinuria due to methylentetrahydrofolate reductase deficiency (see below). The absence of hypermethioninemia differentiates both of these conditions from cystathionine β-synthase deficiency (see above). Renal artery thrombosis, hemolytic uremic syndrome, pulmonary hypertension and optic nerve atrophy have been reported in some patients with these defects.

**Diagnosis** is established by complementation studies performed in cultured fibroblasts. Prenatal diagnosis has been accomplished by studies in amniotic cell cultures. These conditions (cblI, cblG, and cblD variant 1) are inherited as autosomal recessive traits. The gene for cblI is MTRR, encoding methionine synthase reductase (located on chromosome 5p15.3-p15.2) and the gene for cblG is MTR, encoding methionine synthase (located on chromosome 1q43); cblD variant 1 is caused by mutations affecting the C-terminal of the MMADHC gene (located on chromosome 2q23.2). Several disease-causing mutations, including a common missense mutation (P1173L) in the MTR gene, have been described.

**Treatment** with vitamin B₁₂ in the form of hydroxycobalamin (1-2 mg/24 hr) is used to correct the clinical and biochemical findings. Results vary among both diseases and sibships.

Defects causing both homocystinuria and methylmalonic acidemias are discussed in Chapter 85.6.

**Homocystinuria Caused by Deficiency of Methylentetrahydrofolate Reductase**

This enzyme reduces 5,10-methylentetrahydrofolate to form 5-methyltetrahydrofolate, which provides the methyl group needed for remethylation of homocysteine to methionine (see Fig. 85-3).

The severity of the enzyme defect and the clinical manifestations varies considerably in different families. Clinical findings vary from apnea, seizure, microcephaly, coma, and death to developmental delay, ataxia, and motor abnormalities or even psychiatric manifestations. Premature vascular disease or peripheral neuropathy has been reported as the only manifestation of this enzyme deficiency in some patients. Adults with severe enzyme deficiency may even be completely asymptomatic. Exposure to the anesthetic nitrous oxide (which inhibits methionine synthase) in patients with methylentetrahydrofolate reductase (MTHFR) deficiency may result in neurologic deterioration and death.

**Laboratory findings** include moderate homocystinemia and homocystinuria. The methionine concentration is low or low normal. This finding differentiates this condition from classic homocystinuria caused by cystathionine β-synthase deficiency. Absence of megaloblastic anemia distinguishes this condition from homocystinuria caused by methylcobalamin formation (see above). Thromboembolism of vessels has also been observed in these patients. Diagnosis may be confirmed by the enzyme assay in cultured fibroblasts or leukocytes or by finding causal mutation in the MTHFR gene.

A number of polymorphisms have been described in the MTHFR gene. Two of these (677C → T and 1298A → C) may affect levels of plasma total homocysteine and have been studied as possible risk factors for a wide variety of medical conditions, ranging from birth defects to vascular disease and even cancer, Alzheimer disease, and death from leukemia. To date, the best data support a role for 677C → T polymorphism as a risk factor for neural tube defects. Although a clinical test for this polymorphism is widely available, its predictive value in any given individual has yet to be determined.

**Treatment** of severe MTHFR deficiency with a combination of folic acid, vitamin B₁₂, vitamin B₁₉, methionine supplementation, and betaine has been tried. Of these, early treatment with betaine seems to have the most beneficial effect.

The condition is inherited as an autosomal recessive trait; the gene for the enzyme has been located on chromosome 1p36.3 and many disease-causing mutations have been reported in the MTHFR gene. Prenatal diagnosis can be offered by measuring MTHFR enzyme activity in cultured chorionic villus cells or amniocytes, by linkage analysis in informative families, or by DNA analysis of the mutation.

**HYPERMETHIONINEMIA**

**Primary (Genetic) Hypermethioninemia**

Elevation of plasma level of methionine occurs in the following genetic conditions:

1. **Classic homocystinuria** (see above).
2. **Hepatic methionine adenosyltransferase (MAT I/MAT III) deficiency:** This enzyme, which has 2 isoforms, MAT I (tetrameric) and MAT III (dimeric), is encoded by a single gene (MAT 1A) and is involved in the first step of methionine catabolism (see Fig. 85-3). Another structurally similar enzyme, MAT II, is encoded by a different gene (MAT 2A on chromosome 2p11.2) and is expressed predominately in nonhepatic tissues (kidney, brain, lymphocytes). Deficiency of MAT I/MAT III causes hypermethioninemia without homocystinuria. The majority of these patients have been diagnosed in the neonatal period through screening for homocystinuria. Most affected individuals have residual enzyme activity and remain asymptomatic throughout life despite persistent hypermethioninemia. Some complain of an unusual offensive odor to their breath (boiled cabbage). A few patients with complete enzyme deficiency have had neurologic abnormalities related to demyelination (intellectual disability, dystonia, dyspraxia).

Laboratory studies reveal markedly elevated levels of plasma methionine with a low level of S-adenosylmethionine and normal concentrations of S-adenosylhomocysteine and homocysteine. These findings differentiate this condition from other causes of hypermethioninemia.

No uniformly accepted therapeutic regimen has yet emerged. Diets low in methionine result in lowering of plasma methionine, but the advisability of such diets has been questioned since lowering of the plasma methionine level causes further lowering of S-adenosylmethionine in the body.
3. **Glycine N-methyltransferase deficiency**: Although there are many methyltransferases present in the body, glycine N-methyltransferase is the critical one for catabolism of S-adenosylmethionine to S-adenosylhomocysteine (see Fig. 85-3). Three patients with deficiency of this enzyme have been reported to date. Clinically, patients were asymptomatic except for mild hepatomegaly and elevated serum levels of transaminases. Other laboratory findings included hypermethioninemia and very high...
levels of serum S-adenosylmethionine. No specific treatment has yet been identified. The condition seems to be inherited as an autosomal recessive trait; the gene for the enzyme (GNMT) is on chromosome 6p21.1.

4. **Adenosylhomocysteine hydrolase deficiency:** Deficiency of this enzyme (see Fig. 85-3) has been reported in 6 patients from 5 different families. Psychomotor retardation and severe hypotonia were common clinical findings in affected individuals. Laboratory studies included elevated levels of serum creatine kinase, hyperalbininemia (causing fetal hydrops in 1 family), hypophosphatemia, and markedly elevated levels of serum S-adenosylhomocysteine with moderate elevations of plasma methionine and S-adenosylmethionine. Marked elevation in S-adenosylhomocysteine has been thought to cause inhibition of methyltransferases, including those involved in synthesis of creatine (see Fig. 85-10) and choline, resulting in their deficiencies. MRI of the brain showed delayed myelination of the white matter. Treatment with a low methionine diet in conjunction with creatine and phosphatidylcholine shows encouraging results in some patients.

5. **Tyrosinemia type I** (see Chapter 85.2).

6. **Citrin deficiency** (see Chapter 85.12).

### Acquired (Nongenetic) Hypermethioninemia

Hypermethioninemia occurs in premature and some full-term infants receiving high-protein diets, in whom it may represent delayed maturation of the enzyme MAT. Lowering the protein intake usually resolves the abnormality. It is also commonly found in patients with various forms of liver disease.

### CYSTATHIONINEMIA (CYSTATHIONINURIA)

Secondary cystathioninuria occurs in patients with vitamin B6, or B12 deficiency, liver disease (particularly damage caused by galactosemia), thryrotoxicism, hepatoblastoma, neuroblastoma, ganglioblastoma, or defects in remethylation of homocysteine.

Cystathionase deficiency results in massive cystathioninuria and mild to moderate cystathioninemia; cystathionine is not normally detectable in blood. Deficiency of this enzyme is inherited as an autosomal recessive trait and its prevalence is estimated to be about 1 in 14,000 live births. Affects subjects with a wide variety of clinical manifestations have been reported. Lack of a consistent clinical picture and the presence of cystathioninuria in a number of individuals free of clinical findings suggest that cystathionase deficiency may be of no clinical significance. A majority of reported cases are responsive to oral administration of large doses of vitamin B6 (≥100 mg/24 hr). When cystathioninuria is discovered in a patient, vitamin B6 treatment seems indicated, but its beneficial effect has not been established. The gene encoding for cystathionase (CTH) is located on chromosome 16q31.1.

### Sulfite Oxidase Deficiency (Molybdenum Cofactor Deficiency)

At the last step in cysteine metabolism, sulfite is oxidized to sulfate by sulfite oxidase, and the sulfate is excreted in the urine (see Fig. 85-3). This enzyme requires a molybdenum-pterin complex named molybdenum cofactor. This cofactor is also necessary for the function of 2 other enzymes in humans: xanthine dehydrogenase (which oxidizes xanthine and hypoxanthine to uric acid) and aldehyde oxidase (involved in oxidizing a number of natural compounds and drugs). Three enzymes, encoded by 3 different genes (MOCS1, MOCS2, and SUOX) are involved in the synthesis of the cofactor. The genes for these enzymes are mapped to chromosomes 6p21.2, 5q11.2, and 14q23.3, respectively. Deficiency of any of the 3 enzymes causes cofactor deficiency with identical phenotype. Most patients, who were originally diagnosed as having sulfite oxidase deficiency, have been proven to have molybdenum cofactor deficiency. Both conditions are inherited as autosomal recessive traits. The gene for sulfite oxidase (SUOX) is on chromosome 12q13.2.

The enzyme and or the cofactor deficiencies produce identical clinical manifestations. Refusal to feed, vomiting, severe intractable seizures (tonic, clonic, myoclonic), cortical atrophy with subcortical multicystic lesions, and severe developmental delay may develop within a few weeks after birth. Bilateral dislocation of ocular lenses is a common finding in patients who survive the neonatal period. The intractable seizures seen in this condition are, in large part, a consequence of secondary vitamin B6 dependency. The accumulation of sulfites in body fluids in this condition causes the inhibition of antiguinuin enzyme which is necessary for conversion of α-aminoacidic semialdehyde to α-aminoacidic acid; the resultant accumulation of α-aminoacidic semialdehyde and its cyclic form P6C causes the inactivation of pyridoxal-5-phosphate (active form of vitamin B6) and, hence, the vitamin B6-dependent epilepsy (see also Chapter 85.14).

These children excrete large amounts of sulfite, thiosulfate, S-sulfocysteine, xanthine, and hypoxanthine in their urine. Urinary and serum levels of uric acid and urinary concentration of sulfate are diminished. Fresh urine should be used for screening purposes and for quantitative measurements of sulfite, because oxidation of sulfite to sulfate at room temperature may produce false-negative results. Increased concentrations of α-aminoacidic semialdehyde and its cyclic form, P6C, and piperacilic acid are present in the CSF, plasma, and urine.

**Diagnosis** is confirmed by measurement of sulfite oxidase and molybdenum cofactor in fibroblasts and liver biopsies, respectively or by DNA studies. Prenatal diagnosis is possible by performing an assay of sulfite oxidase activity in cultured amniotic cells, in samples of chorionic villi or by DNA studies.

No effective **treatment** is available; large doses of vitamin B6 (5-100 mg/kg) result in dramatic alleviation of seizures but do not seem to alter the devastating neurologic outcome. Most children die in the 1st 2 yr of life. One patient had an initial response to cyclic pyranopterin monophosphate (cFMP). The prevalence of these deficiencies in the general population is not known.

**Bibliography is available at Expert Consult.**

### 85.5 Tryptophan

**Iraj Rezvani**

Tryptophan is an essential amino acid and a precursor for nicotinic acid (niacin) and serotonin (Fig. 85-5). The genetic disorders of metabolism of serotonin, one of the major neurotransmitters, are discussed in Chapter 85.11.

### HARTNUP DISORDER

In this autosomal recessive disorder, named after the first affected family, there is a defect in the transport of monoamino-monocarboxylic amino acids (neutral amino acids), including tryptophan, by the intestinal mucosa and renal tubules. The transporter protein for these amino acids (B0AT1) is encoded by the SLC6A19 gene located on chromosome 5p15.33. Two chemically close transcription factors, angiotensin-converting enzyme (ACE2) in the intestine and renal tubules, and collectrin in the renal tubules, are required for expression of B0AT1 transporter protein by the SLC6A19 gene. The mutated gene in patients with Hartnup disorder, unable to interact with the above...
Bibliography


Defects in Metabolism of Amino Acids

Bibliography


transcription factors, results in deficiency of B0AT1 protein either in the intestine or in the renal tubules or in both. This explains the absence of renal or intestinal transport defect seen in some affected families. Decreased intestinal absorption of tryptophan in conjunction with its increased renal loss is believed to cause reduced availability of tryptophan for niacin synthesis in affected individuals. Most children with Hartnup disorder remain asymptomatic. The major clinical manifestation in the rare symptomatic patient is cutaneous photosensitivity. The skin becomes rough and red after moderate exposure to the sun, and with greater exposure, a pellagra-like rash may develop. The rash may be pruritic, and a chronic eczema may develop. The skin changes have been reported in affected infants as young as 10 days of age. Some patients may have intermittent ataxia manifested as an unsteady, wide-based gait. The ataxia may last a few days and usually recovers spontaneously. Mental development is usually normal. Two individuals in the original kindred were cognitively impaired. Episodic psychiatric manifestations such as irritability, emotional instability, depression, and suicidal tendencies, have been observed; these changes are usually associated with bouts of ataxia. Short stature and atrophic glossitis are seen in some patients.

Most children diagnosed with Hartnup disorder by neonatal screening have remained asymptomatic. This indicates that other factors are also involved in pathogenesis of the clinical condition.

The main laboratory finding is aminoaciduria, which is restricted to neutral amino acids (alanine, serine, threonine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, histidine). Urinary excretion of proline, hydroxyproline, and arginine remains normal. This finding differentiates Hartnup disorder from other causes of generalized aminoaciduria, such as Fanconi syndrome. Plasma concentrations of neutral amino acids are usually normal. This seemingly unexpected finding occurs because these amino acids are absorbed as dipeptides and the transport system for small peptides is intact in Hartnup disorder. The indole derivatives (especially indican) may be found in large amounts in some patients, owing to bacterial breakdown of unab sorbed tryptophan in the intestines.

Diagnosis is established by the striking intermittent nature of symptoms and the previously described urinary findings.

Treatment with nicotinic acid or nicotinamide (50-300 mg/24 hr) and a high-protein diet results in a favorable response in symptomatic patients. Because of the intermittent nature of the clinical manifestations, the efficacy of these treatments is difficult to evaluate. The prevalence of the disorder is estimated to be 1 in 20,000 to 1 in 30,000 live births. Normal outcome both for mother and fetus is reported in affected pregnant women.

Bibliography is available at Expert Consult.

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85.6 Valine, Leucine, Isoleucine, and Related Organic Acidemias

Iraj Rezvani and David S. Rosenblatt

The early steps in the degradation of these 3 essential amino acids, the branched-chain amino acids, are similar (see Fig. 85-4). The intermediate metabolites are all organic acids, and deficiency of any of the degradative enzymes, except for the transaminases, causes acidosis; in such instances, the organic acids proximal to the enzymatic block accumulate in body fluids and are excreted in the urine. These disorders commonly cause metabolic acidosis, which usually occurs in the first few days of life. Although most of the clinical findings are nonspecific, some manifestations may provide important clues to the nature of the enzyme deficiency. Figure 85-6 presents an approach to infants suspected of having an organic acidemia. Definitive diagnosis is usually established by identifying and measuring specific organic acids in body fluids (blood, urine), by the enzyme assay, and by identification of the mutant gene.

Organic acidemias are not limited to defects in the catabolic pathways of branched-chain amino acids. Disorders causing accumulation of other organic acids include those derived from lysine (see Chapter 85.14), those associated with lactic acid (see Chapter 87), and dicarboxylic acidemias associated with defective fatty acid degradation (see Chapter 86.1).

MAPLE SYRUP URINE DISEASE

Decarboxylation of leucine, isoleucine, and valine is accomplished by a complex enzyme system (branched-chain α-ketoacid dehydrogenase [BCKDH]) using thiamine (vitamin B1) pyrophosphate as a coenzyme. This mitochondrial enzyme consists of 4 subunits: E1α, E1β, E2, and E3. The E2 subunit is shared with 2 other dehydrogenases in the body, namely pyruvate dehydrogenase and α-ketoglutarate dehydrogenase. Deficiency of any of these subunits causes maple syrup urine disease (MSUD) (see Fig. 85-4), named after the sweet odor of maple syrup found in body fluids, especially urine. Clinical conditions caused by defects in E1α, E1β, E2, and E3 are designated as MSUD type IA, type IB, type 2, and type 3 respectively. This classification, however, is not very helpful clinically because the severity of clinical manifestations does not correlate with or correspond specifically to any single type. An affected infant with type 1A defect can have clinical manifestations ranging from relatively mild to very severe. A more useful classification, based on clinical findings and response to thiamine administration, has identified 5 phenotypes of MSUD as follows:

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Figure 85-5 Pathways in the metabolism of tryptophan. PKU* indicates hyperphenylalaninemia caused by tetrahydrobiopterin deficiency (see Fig. 85-1). Enzymes: (1) Tryptophan hydroxylase, (2) aromatic l-αmino acid decarboxylase (AADC), (3) monoamine oxidase (MAO).
Bibliography
Clinical approach to MSUD, to infants

Soon as possible so as to reverse the patient's catabolic state. Cerebral calories and nutrients should be provided intravenously or orally as of therapy in critically ill infants and should be instituted promptly; peritoneal dialysis or, preferably, hemodialysis is the most effective mode is poor, hydration alone may not produce a rapid improvement. Peri-
imaging of the brain. The enzyme activity can be measured in leukocytes ing age, hypomyelination and cerebral atrophy may be seen in neuro-

terminal capsule. After recovery from the acute state and with advanc-

ing during the acute state may show cerebral edema, which is most prominent in the cerebellum, dorsal brainstem, cerebral peduncle, and prominence in the interictal period.

Generalized seizures and coma may ensue within a few days. Physical examination reveals hypotonia and muscular rigidity with severe opisthotonus. Periods of hypotonia may alternate with bouts of flaccidity manifested as repetitive movements of the extremities (boxing and bicycling). Neurologic findings are often mistakenly thought to be caused by generalized spasticity and meningitis. Cerebral edema may be present; convulsions occur in most infants, and hypo-
glycemia is common. In contrast to most hypoglycemic states, correction of the blood glucose concentration does not improve the clinical condition. Aside from the serum glucose, routine laboratory findings are usually unremarkable, except for varying degrees of metabolic acido-

osis. Death usually occurs in untreated patients in the first few weeks or months of life.

Diagnosis is often suspected because of the peculiar odor of maple syrup found in urine, sweat, and cerumen (see Fig. 85-6). It is usually confirmed by amino acid analysis showing marked elevations in plasma levels of leucine, isoleucine, valine, and alloisoleucine (a stereo-specific isomer of isoleucine not normally found in blood) and depression of alanine. Leucine levels are usually higher than those of the other 3 amino acids. Plasma concentrations of leucine, isoleucine, and valine and their respective ketoacids. These ketoacids may be detected qualitatively by adding a few drops of 2,4-dinitrophenylhydrazine reagent (0.1% in 0.1N HCl) to the urine; a yellow precipitate of 2,4-dinitrophenylhydrazone, is formed in a positive test. Neuroimag-
ing during the acute state may show cerebral edema, which is most prominent in the cerebellum, dorsal brainstem, cerebral peduncle, and internal capsule. After recovery from the acute state and with advancing age, hypomyelination and cerebral atrophy may be seen in neuro-

imaging of the brain. The enzyme activity can be measured in leukocytes and cultured fibroblasts.

Treatment of the acute state is aimed at hydration and rapid removal of the branched-chain amino acids and their metabolites from the tissues and body fluids. Because renal clearance of these compounds is poor, hydration alone may not produce a rapid improvement. Peri-
toneal dialysis or, preferably, hemodialysis is the most effective mode of therapy in critically ill infants and should be instituted promptly; significant increases in plasma levels of leucine, isoleucine, and valine are usually seen within 24 hr of institution of treatment. Sufficient calories and nutrients should be provided intravenously or orally as soon as possible so as to reverse the patient's catabolic state. Cerebral edema, if present, may need to be treated with mannitol, diuretics (e.g., furosemide), or hypertonic saline.

Treatment after recovery from the acute state requires a diet low in branched-chain amino acids. Synthetic formulas devoid of leucine, isoleucine, and valine are available commercially. Because these amino acids cannot be synthesized endogenously, small amounts of them should be added to the diet; the amount should be titrated carefully by performing frequent analyses of the plasma amino acids. A clinical condition resembling acrodermatitis enteropathica (see Chapter 671) occurs in affected infants whose plasma isoleucine concentration becomes very low; addition of isoleucine to the diet causes a rapid and complete recovery. Patients with MSUD should remain on the diet for the rest of their lives. Liver transplantation has been performed in a number of patients with classic MSUD with promising results. These children have been able to tolerate a normal diet.

The long-term prognosis of affected children remains guarded. Severe ketoacidosis, cerebral edema, and death may occur during any stressful situation such as infection or surgery, especially in mid-

childhood. Cognitive and other neurologic deficits are common sequelae.

Intermediate (Mild) Maple Syrup Urine Disease

In this form, affected children develop milder disease after the neonatal period. Clinical manifestations are insidious and limited to the CNS. Patients have mild to moderate intellectual disability (usually after 5 mo of age) with or without seizures. They have the odor of maple syrup and excrete moderate amounts of the branched-chain amino acids and their ketoacid derivatives in the urine. In this form, affected children develop milder disease after the neonatal period. Clinical manifestations are insidious and limited to the CNS. Patients have mild to moderate intellectual disability (usually after 5 mo of age) with or without seizures. They have the odor of maple syrup and excrete moderate amounts of the branched-chain amino acids and their ketoacid derivatives in the urine. Plasma concentrations of leucine, isoleucine, and valine are moderately increased whereas those of lactate and pyruvate are normal. These children are commonly diagnosed during an intercurrent illness when signs and symptoms of classic MSUD may occur. The dehydrogenase activity is 3-40% of normal. Because patients with thiamine-responsive MSUD usually have manifestations similar to those seen in the mild form, a trial of thiamine therapy is recommended. Diet therapy, similar to that of classic MSUD, is needed.

Intermittent Maple Syrup Urine Disease

In this form of MSUD, seemingly normal children develop vomiting, odor of maple syrup, ataxia, lethargy, and coma during any stress or catabolic state such as infection or surgery. During these attacks, labor-
atory findings are indistinguishable from those of the classic form, and death may occur. Treatment of the acute attack of intermittent

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**Table 85-2**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Common features</th>
<th>Diagnosis</th>
<th>Treatment after recovery</th>
<th>Long-term prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSUD</td>
<td>Refusal to feed, vomiting, ketosis, characteristic odor</td>
<td>Amino acid analysis showing elevated plasma levels of leucine, isoleucine, valine, and alloisoleucine</td>
<td>Diet low in branched-chain amino acids, synthetic formulas devoid of leucine, isoleucine, and valine</td>
<td>guarded</td>
</tr>
<tr>
<td>3-Hydroxy-3-methylglutaric aciduria</td>
<td>3-HMG CoA dehydrogenase deficiency</td>
<td></td>
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<td>Acyl-CoA dehydrogenase deficiencies</td>
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<td>HMG-CoA synthetase deficiency</td>
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**Figure 85-6** Clinical approach to infants with organic acidemia. Asterisks indicate disorders in which patients have a characteristic odor (see text and Table 85-2). MSUD, maple syrup urine disease.
MSUD is similar to that of the classic form. After recovery, although a normal diet is tolerated, a diet low in branched-chain amino acids is recommended. Activity of the dehydrogenase in patients with the intermittent form is higher than in the classic form and may reach 40% of the normal activity.

**Thiamine-Responsive Maple Syrup Urine Disease**

Some children with mild or intermediate forms of MSUD who are treated with high doses of thiamine have dramatic clinical and biochemical improvement. Although some respond to treatment with thiamine at 10 mg/24 hr, others may require as much as 200 mg/24 hr for at least 3 wk before a favorable response is observed. These patients also require diets deficient in branched-chain amino acids. The enzymatic activity in these patients is 30–40% of normal.

**Maple Syrup Urine Disease Caused by a Deficiency of E$_2$ Subunit (Maple Syrup Urine Disease Type 3)**

This is a very rare disorder. Patients develop lactic acidosis in addition to signs and symptoms similar to those of intermediate MSUD because the E$_2$ subunit is also a component of pyruvate dehydrogenase and α-ketoglutarate dehydrogenase. Progressive neurologic impairment manifested by hypotonia and developmental delay occurs after 2 mo of age. Abnormal movements progress to ataxia. Death may occur in early childhood.

**Laboratory findings** include persistent lactic acidosis with high levels of plasma lactate, pyruvate, and alanine. Plasma concentrations of branched-chain amino acids are moderately increased. Patients excrete large amounts of lactate, pyruvate, α-glutamate, and the 3-branched-chain ketoacids in their urine.

No effective treatment is available. Dietary restrictions of branched-chain amino acids and treatment with high doses of thiamine, biotin, and lipoic acid have been ineffective.

**Genetics and Prevalence of Maple Syrup Urine Disease**

All forms of MSUD are inherited as an autosomal recessive trait. The gene for each subunit resides on different chromosomes. The gene for E$_{1a}$ (BCKDHA) is on chromosome 19q13.1-q13.2; that for E$_{1b}$ (BCKDHB) is on chromosome 6q14.1; the gene for E$_{2}$ (DBT) is on chromosome 1p21.2; and that for E$_{3}$ (DDL) is on chromosome 7q31.1. Many different disease-causing mutations (>160) have been identified in patients with different forms of MSUD. A given clinical phenotype is caused by a variety of genotypes; an example, patients from different pedigrees with the classic form of MSUD have been shown to have mutations in genes for E$_{1a}$, E$_{1b}$, or E$_{2}$ subunits. The exception is the thiamine-responsive MSUD that is known to be caused by mutations in the E$_{2}$ gene in all reported cases to date. Most patients are compound heterozygotes inheriting 2 different mutant alleles. Mutations in genes for E$_{1a}$ (45%) and E$_{1b}$ (35%) account for approximately 80% of cases.

The prevalence is estimated at 1 in 185,000 live births. The classic form of MSUD is more prevalent in the Old Order Mennonites in the United States (in the United States). Isovaleric acidemia is inherited as an autosomal recessive trait (see Chapter 84). Isovaleryl CoA dehydrogenase (see Fig. 85-4). Clinically, two forms of the condition are recognized in symptomatic patients: the acute form and the chronic intermittent form.

**ISOOVALERIC ACIDEMIA**

This condition is caused by the deficiency of the enzyme isovaleryl CoA dehydrogenase (see Fig. 85-4). Clinically, two forms of the condition are recognized in symptomatic patients: the acute form and the chronic intermittent form.

**Clinical manifestations** in the acute form include vomiting and severe acidosis in the first 2 wk of life. Lethargy, convulsions, and coma may ensue, and death may occur if proper therapy is not initiated. The vomiting may be severe enough to suggest pyloric stenosis. The characteristic odor of “sweaty feet” may be present (in body sweat and corns, but not in the urine; see Fig. 85-6). Infants who survive this acute episode will go on to have the chronic intermittent form later in life. In the chronic intermittent form of the disease, the first clinical manifestations (vomiting, lethargy, acidosis or coma) may not appear until the child is a few months or a few years old. In both forms, acute episodes of metabolic decompensations may occur during a catabolic state such as an infection. Acute episodes may be mistaken for diabetic ketoacidosis. With worldwide application of newborn screening technology (see Chapter 84) it is now becoming clear that the clinical spectrum in affected patients can range from completely asymptomatic to the acute form. Older siblings of symptomatic newborn infants have been reported with identical genotype and biochemical abnormalities but without any clinical manifestations.

**Laboratory findings** during the acute attacks include ketoacidosis, neutropenia, thrombocytopenia, and occasionally pancyclopentenia. Hypocalcemia, hyperglycemia, and moderate to severe hyperammonemia may be present in some patients. Increases in plasma ammonia may suggest a defect in the urea cycle (see Chapter 85.12). In urea cycle defects, the infant is not acidic (see Fig. 85-6).

**Diagnosis** is established by demonstrating marked elevations of isovaleric acid and its metabolites (isovalerylglucine, 3-hydroxyisovaleric acid) in body fluids, especially urine. The main compound in plasma is isovalerylcarnitine, which can be measured even in a few drops of dried blood on a filter paper. Diagnosis can be confirmed by measurement of the enzyme activity in cultured skin fibroblasts or by the identification of the mutant gene.

**Treatment** of the acute attack is aimed at hydration, reversal of the catabolic state (by providing adequate calories orally or intravenously), correction of metabolic acidosis (by infusing sodium bicarbonate), and removal of the excess isovaleric acid. Because isovalerylglucine has a high urinary clearance, administration of glycine (250 mg/kg/24 hr) is recommended to enhance formation of isovalerylglucine. L-Carnitine (100 mg/kg/24 hr orally) also increases removal of isovaleric acid by forming isovaleryl carnitine, which is excreted in the urine. In patients with significant hyperammonemia (blood ammonia >200 μM), measures that reduce blood ammonia should be employed (see Chapter 85.12). Exchange transfusion and peritoneal dialysis may be needed if the previously described measures fail to induce significant clinical and biochemical improvement. After recovery from the acute attack, the patient should receive a low-protein diet (1.0-1.5 g/kg/24 hr) and should be given glycine and carnitine supplements. Pancreatitis (acute or recurrent forms) has been reported in survivors. Normal development can be achieved with early and proper treatment.

Prenatal diagnosis may be accomplished by measuring isovalerylglucine in amniotic fluid, by enzyme assay in cultured amniocytes, or by identification of the mutant gene. Successful pregnancy with favorable outcomes both for the mother and the infant has been reported.

**MULTIPLE CARBOXYLASE DEFICIENCIES**

**DEFECTS IN UTILIZATION OF BIOTIN**

Biotin is a water-soluble vitamin that is a cofactor for all 4 carboxylase enzymes in humans: pyruvate carboxylase, acetyl CoA carboxylase,
propionyl CoA carboxylase, and 3-methylcrotonyl CoA carboxylase. The latter 2 are involved in the metabolic pathways of leucine, isoleucine, and valine (see Fig. 85-4).

Dietary biotin is bound to proteins; free biotin is generated in the intestine by the action of digestive enzymes, by intestinal bacteria, and perhaps by biotinidase. The latter enzyme, which is found in serum and most tissues in the body, is also essential for the recycling of biotin in the body by releasing it from the apoenzymes (carboxylases; see Fig. 85-4). Free biotin must form a covalent peptide bond with the apoprotein of the 4 carboxylases to form the activated enzyme (holocarboxylase). This binding is catalyzed by holocarboxylase synthetase. Deficiencies in this enzyme activity or in biotinidase result in malfunction of all the carboxylases and in organic acidaemia.

**Holocarboxylase Synthetase Deficiency (Multiple Carboxylase Deficiency Neonatal or Early Form)**

Infants with this rare autosomal recessive disorder become symptomatic in the first few weeks of life. Symptoms may appear as early as a few hours after birth to 21 mo of age. Clinically, the affected infants who seem normal at birth develop breathing difficulties (tachypnea and apnea) shortly after birth. Feeding problems, vomiting, and hypotonia are also commonly present. If the condition remains untreated, generalized erythematous rash with exfoliation and alopecia (partial or total), failure to thrive, irritability, seizures, lethargy, and even coma may occur. Developmental delay is common. Immune deficiency manifests with susceptibility to infection. The urine may have a peculiar odor, which has been described as similar to tomcat urine. The rash, when present, differentiates this condition from other organic acidaemias (see Fig. 85-6).

**Laboratory findings** include metabolic acidosis, ketosis, hyperammonemia, and the presence of a variety of organic acids (lactic acid, propionic acid, 3-methylcrotonic acid, 3-methylcrotonylglycine, tiglylglycine, methylcitrate, and 3-hydroxyisovaleric acid) in body fluids. Diagnosis is confirmed by the enzyme assay in lymphocytes or cultured fibroblasts or by identification of the mutant gene. Most mutations cause the enzyme to have an increased $K_m$ (Michaelis-Menten dissociation constant) for biotin; the enzyme activity in such patients can be restored by the administration of large doses of biotin.

**Treatment** with biotin (10 mg/day orally) usually results in an improvement in clinical manifestations and may normalize the biochemical abnormalities. Early diagnosis and treatment are critical to prevent irreversible neurologic damage. In some patients, however, complete resolution may not be achieved even with large doses (up to 80 mg/day) of biotin.

The gene for holocarboxylase synthetase (HLCS) is located on chromosome 21q22.1 and many disease-causing mutations have been identified in different families. Prenatal diagnosis has been accomplished by assaying enzyme activity in cultured amniotic cells and by measurement of intermediate metabolites (3-hydroxyisovalerate and methylcitrate) in amniotic fluid or by DNA analysis. Pregnant mothers who had previous offspring with holocarboxylase synthetase deficiency have been treated with biotin late in pregnancy. Affected infants were normal at birth, but the inefficacy of the treatment as related to the outcome remains unclear.

**Biotinidase Deficiency (Multiple Carboxylase Deficiency—Juvenile or Late Form)**

The absence of biotinidase results in biotin deficiency. Infants with this deficiency may develop clinical manifestations similar to those seen in infants with holocarboxylase synthetase deficiency but, unlike the latter, symptoms may appear later when the child is several months or years old; symptoms may develop as early as 1 wk of age. Therefore, the term “late form” does not apply to all cases and can be misleading. The delay is presumably because of the presence of sufficient free biotin derived from the mother or the diet. Clinical manifestations are mostly confined to skin and the nervous system. Atopic or seborrheic dermatitis, candidiasis, alopecia, ataxia, seizures (usually myoclonic type), hypotonia, developmental delay, optic atrophy, sensorineural hearing loss, and immunodeficiency (from T-cell abnormalities) may occur. A small number of children with intractable seborrheic dermatitis and partial (15-30% activity) deficiency of the enzyme, in whom the dermatitis resolved with biotin therapy, have been reported; these children were otherwise asymptomatic. Asymptomatic children and adults with this enzyme deficiency have been identified in screening programs. Most of these individuals have been shown to have partial deficiency of the enzyme activity. With the advent of mass screening of newborn infants and early identification and treatment of the affected patients, the clinical disease is predicted to become extinct.

**Laboratory findings** and the pattern of organic acids in body fluids resemble those associated with holocarboxylase synthetase deficiency (see above). Diagnosis can be established by measurement of the enzyme activity in the serum or by the identification of the mutant gene.

**Treatment** with free biotin (5-20 mg/24 hr) results in a dramatic clinical and biochemical response. Treatment with biotin is also suggested for individuals with partial biotinidase deficiency.

The prevalence of this autosomal recessive trait is estimated at 1 in 60,000 live births. The gene for biotinidase (BTD) is located on chromosome 3p25.1 and many disease-causing mutations (approximately 150) have been identified in different families. Prenatal diagnosis is possible by the measurement of the enzyme activity in the amniotic cells or by identification of the mutant gene.

**Multiple Carboxylase Deficiency Because of Dietary Biotin Deficiency**

Acquired deficiency of biotin may occur in infants receiving total parenteral nutrition without added biotin, in patients receiving prolonged anticonvulsant drugs (phenytoin, primidone, carbamazepine) or in children with short bowel syndrome or chronic diarrhea who are receiving formulas low in biotin. Excessive ingestion of raw eggs may also cause biotin deficiency because the protein avidin in egg white binds biotin and makes it unavailable for absorption. Infants with biotin deficiency may develop dermatitis, alopecia, and candidal skin infections.

**ISOLATED 3-METHYLacrotyonyL COENZYME A (CoA) CARBOXYLASE DEFICIENCY**

This enzyme is 1 of 4 carboxylase enzymes in the body that require biotin as a cofactor (see Fig. 85-4). An isolated deficiency of this enzyme must be differentiated from disorders of biotin metabolism (multiple carboxylase deficiency), which causes diminished activity of all 4 carboxylases (see above). 3-Methylcrotonyl CoA carboxylase is a heteroergic enzyme consisting of α (biotin containing) and β subunits.

**Clinical manifestations** are highly variable, ranging from fatal neonatal onset (seizures, hypotonia, acidosis) to completely asymptomatic adults (including mothers of affected newborn infants). In the severe form of the condition, the affected infant who has been seemingly normal develops an acute episode of vomiting, hypotonia, lethargy, and convulsions after a minor infection. The onset is usually between 3 wk and 3 yr of age. Death may occur during the acute episode.

**Laboratory findings** during acute episodes include mild to moderate acidosis, ketosis, severe hypoglycemia, hyperammonemia, and elevated serum levels of liver transaminases. Large amounts of 3-hydroxyisovaleric acid and 3-methylcrotonylglycine are found in the urine. Urinary excretion of 3-methylcrotonic acid is not usually increased in this condition because the accumulated 3-methylcrotonyl CoA is converted to 3-hydroxyisovaleric acid. Severe secondary carnitine deficiency is common. The condition should be differentiated biochemically from multiple carboxylase deficiency (see above) in which lactic acid and metabolites of propionic acid are present in body fluids in addition to 3-hydroxyisovaleric acid. Diagnosis may be confirmed by measurement of the enzyme activity in cultured fibroblasts or by DNA analysis. Documentation of normal activities of other carboxylases is necessary for definitive diagnosis.
Defects

Treatment of acute episodes is similar to that of isovaleric acidemia (see above). Hydration and measures to correct metabolic acidosis and hypoglycemia (by infusing sodium bicarbonate and glucose) should be instituted promptly. Administration of L-carnitine and glycine is also recommended. These patients are unresponsive to biotin therapy. Patients who, in earlier reports, were found to be biotin-responsive were most probably suffering from multiple carboxylase deficiency as a result of biotinidase deficiency (see above). Long-term treatment includes a diet restricted in leucine in conjunction with the oral administration of L-carnitine (75-100 mg/kg/24 hr) and the prevention of catabolic states. Normal growth and development are expected in these patients.

The condition is inherited as an autosomal recessive trait. The gene for α subunit (MCC1) is located on chromosome 3q27.1 and that for the β subunit (MCC2) is mapped to chromosome 5q13.2. Mutation in either of these genes may result in the deficiency of the enzyme activity. Similar phenotypes may be caused by different genotype. Several disease-causing mutations in either gene have been identified in different families. Newborn screening programs using tandem mass spectrometry have identified an unexpectedly high number of infants with 3-methylcrotonyl-CoA carboxylase deficiency (1:50,000). Only a small number (<10%) of the affected infants become symptomatic; none of the symptoms reported so far could be clearly attributed to the degree of enzyme deficiency. These findings have questioned the advisability of including this condition in the routine newborn screening programs because the psychologic and financial burdens may outweigh the potential benefits.

3-METHYLGLUTACONIC ACIDURIA

Six inherited conditions are known to be associated with excessive excretion of 3-methylglutaconic acid in the urine. Deficiency of the enzyme 3-methylglutacanoyl CoA hydratase (see Fig. 85-4) has been documented in only 1 condition (type I). In the other 5 conditions, the enzyme activity is normal despite a modest 3-methylglutaconic aciduria. The reason for increased urinary excretion of 3-methylglutaconic acid in these conditions is not completely understood; although these conditions are caused by mutations in different genes, the gene products are all critical for normal mitochondrial function. Only 3-methylglutacanoylacidurias—types I, II, and III—are discussed here because the clinical pictures of types IV and V (dilated cardiomyopathy with ataxia) are not well delineated.

3-Methylglutacanoyl Aciduria Type I (3-Methylglutacanoyl Coenzyme A Hydratase Deficiency)

See Figure 85-4.

Two main clinical forms of the condition have been described. In the childhood form, nonspecific neurodevelopmental findings such as speech delay or regression, choreoathetoid movements, optic atrophy, and mild psychomotor delay may be present. Metabolic acidosis may occur during a catabolic state. In the adulthood form, affected individuals remain asymptomatic until the 2nd or 3rd decades of life, when a clinical picture of slowly progressing leukoencephalopathy with optic atrophy, dystonia, ataxia, spasticity, and dementia occurs. MRI of the brain typically shows white matter abnormalities that may precede appearance of clinical symptoms by years. Asymptomatic affected children and adults have also been reported. Patients excrete large amounts of 3-methylglutacanoylacid and moderate amounts of 3-hydroxyisovaleric and 3-methylglutaric acids in urine. Deficiency of 3-methylglutacanoyl CoA hydratase has been shown in cultured fibroblasts and lymphoblasts. Treatment with a low leucine diet seems to be indicated even in asymptomatic affected individuals. Beneficial effects of this therapy on the clinical course of the disease remain to be determined. Administration of L-carnitine has resulted in clinical improvement in 1 patient. The condition is inherited as an autosomal recessive trait; the gene for the hydratase enzyme (AUH) is mapped to chromosome 9q22.3.

3-Methylglutacanoyl Aciduria Type II (X-Linked Cardiomyopathy, Neutropenia, Growth Retardation, and 3-Methylglutacanoyl Aciduria with Normal 3-Methylglutacanoyl Coenzyme A Hydratase, Barth Syndrome)

This X-linked mitochondrial condition is caused by deficiency of tafazzin, a mitochondrial protein (enzyme), encoded by TAZ gene. This enzyme is necessary for processing of immature cardiolipin into the mature form (cardiolipin remodeling). Cardiolipin, a mitochondrial phospholipid, is critical for the integrity of inner mitochondrial membrane. Clinical manifestations of this condition, which usually occur in the first year of life in a male infant, include dilated cardiomyopathy (manifested as respiratory distress and heart failure), hypotonia, growth retardation, hypoglycemia, and moderate to severe cyclic neutropenia. The onset of clinical manifestations may be as late as 49 yr of age, but most affected individuals become symptomatic by adolescence. If patients survive infancy, relative improvement may occur with advancing age. Cognitive development is usually normal despite delayed motor function.

Clinical manifestations include mild to moderate increases in urinary excretion of 3-methylglutacanoyl, 3-methylglutaric, and 2-ethylhydracrylic acids. Unlike 3-methylglutacanoyl aciduria type I, urinary excretion of 3-hydroxyisovaleric acid is not elevated. The activity of the enzyme 3-methylglutacanoyl CoA hydratase is normal. Cyclic neutropenia is a common finding. Lactic acidosis, hypoglycemia, low serum cholesterol concentration and abnormal mitochondrial ultrastructure have been shown in some patients. Total cardiolipin and subclasses of cardiolipin are very low in skin fibroblast cultures from these patients. This finding may be useful for establishing the diagnosis.

The condition is inherited as an X-linked recessive trait. The gene (TAZ) has been mapped to chromosome Xq28 and several disease-causing mutations have been identified. The lack of 3-methylglutacanoyl aciduria seen in this condition is thought to be related to the defect in mitochondrial membrane causing the leakage of this organic acid. No effective treatment is available. Older surviving patients may benefit from cardiac transplantation. There are reasons to believe that the condition is perhaps more common than realized; most affected patients remain undiagnosed or misdiagnosed as having viral cardiomyopathy.

3-Methylglutacanoyl Aciduria Type III (Costeff Optic Atrophy Syndrome)

Clinical manifestations in these patients include early onset optic atrophy and later development of choreoathetoid movements, spasticity, ataxia, dysarthria, and mild developmental delay. All reported patients except 1 were Iraqi Jews living in Israel. These patients excrete moderate amounts of 3-methylglutacanoyl and 3-methylglutaric acids. Activity of the enzyme 3-methylglutacanoyl CoA hydratase is normal. The reason for the increased excretion of these organic acids remains unclear. The condition is inherited as an autosomal recessive trait. The gene for this condition (OPA3) is mapped to chromosome 19q13.2-q13.3. Mutation of this gene is believed to cause mitochondrial dysfunction. No effective treatment is available.

β-KETOTHIOIASE (3-OXOTHIOIASE) DEFICIENCY (MITOCHONDRIAL ACETOACETYL COENZYME A THIOLASE [T3] DEFICIENCY)

This reversible mitochondrial enzyme is involved in final steps of catabolism of isoleucine and also in oxidation of fatty acids. It cleaves 2-methylacetoacetoyl CoA to propionyl-CoA plus acetyl-CoA in isoleucine catabolic pathway (see Fig. 85-4). In the fatty acid oxidation pathway, the enzyme generates 2 moles of acetyl-CoA from 1 mole of acetoacetyl-CoA (Fig. 85-7). The same enzyme synthesizes 2-methylacetoylacetate-CoA and acetaoctyl-CoA in the reverse direction (Fig. 85-7).

Clinical manifestations are quite variable, ranging from an asymptomatic course in an adult to severe episodes of acidosis starting in the
1st yr of life. Typically, these children have intermittent episodes of unexplained ketosis and acidosis. These episodes usually occur after an intercurrent infection and respond quickly to intravenous fluids and bicarbonate therapy. Mild to moderate hyperammonemia may also be present during attacks. Both hypoglycemia and hyperglycemia have been reported in isolated cases. The child may be completely asymptomatic between episodes and may tolerate a normal protein diet well. Cognitive development is normal in most children. The episodes may be misdiagnosed as salicylate poisoning because of the similarity of the clinical findings and the interference of elevated blood levels of acetoacetate and 3-hydroxybutyrate assaying for salicylate.

**Laboratory findings** during the acute attack include acidosis, ketosis, and hyperammonemia. The urine contains large amounts of 2-methylacetoacetate and its decarboxylated products butanone, 2-methyl-3-hydroxybutyrate, and tiglylglycine. Lower concentrations of these urinary metabolites persist during the seemingly well periods. Some 11q22.3.

**Treatment** of acute episodes includes hydration and infusion of bicarbonate to correct the acidosis; a 10% glucose solution with the appropriate electrolytes and intravenous lipids may be used to minimize the catabolic state. Restriction of protein intake (1-2 g/kg/24 hr) is recommended for long-term therapy. Oral L-carnitine (50-100 mg/kg/24 hr) is also recommended to prevent possible secondary carnitine deficiency. Long-term prognosis for achieving normal life seems very favorable. Three reported patients graduated from high school and 1 has attended college. All patients continued to have abnormal metabolites in body fluids. Successful pregnancy with normal outcomes for both mother and infant has been reported.

The pathogenesis of ketosis in this condition is not adequately explained because, in this enzyme deficiency, one expects impaired ketone formation (see Fig. 85-7). It is postulated that excess acetoacetate CoA produced from other sources is used as a substrate for 3-hydroxy-3-methylglutaryl (HMG) CoA synthesis in the liver.

This condition is inherited as an autosomal recessive trait and may be more prevalent than has been appreciated. It is most prevalent in Tunisia. The gene (ACAT1) for this enzyme (T2) is located on chromosome 11q22.3.

**CYTOSOLIC ACETOACETYL COENZYME A THIOLASE DEFICIENCY**

This enzyme catalyzes the cytosolic production of acetoacetyl CoA from 2 moles of acetyl CoA (see Fig. 85-7). Cytosolic acetoacetyl CoA is the precursor of hepatic cholesterol synthesis. Cytosolic acetoacetyl CoA thiolase is a completely different enzyme from mitochondrial thiolase (see above and Fig. 85-4). Clinical manifestations in patients with this very rare enzyme deficiency are similar to those in patients with mevalonic acidemia (see below). Severe progressive developmental delay, hypotonia, and choreoathetoid movements develop in the first few months of life. Laboratory findings are nonspecific; elevated levels of lactate, pyruvate, acetocacetate, and 3-hydroxybutyrate may be found in blood and urine. One patient had normal levels of acetoacetate and 3-hydroxybutyrate. Diagnosis can be established by demonstrating a deficiency in cytosolic thiolase activity in liver biopsy or in cultured fibroblasts or by DNA analysis. No effective treatment is available. The gene (ACAT2) for this condition is mapped to chromosome 6q25.3.
**Defects in Metabolism of Amino Acids**

This enzyme catalyzes synthesis of 3-hydroxy-3-methylglutaryl (HMG)-CoA from acetocetoyl CoA in the mitochondria. This is a critical step in ketone body synthesis in the liver (see Fig. 85-7). A few patients with deficiencies of this enzyme have been reported. All patients have had similar presentations and outcomes. Signs and symptoms of acute hypoglycemia have occurred after an acute illness (gastroenteritis). Age at presentation has ranged from 18 mo to 6 y. All children were asymptomatic before the episodes and remained normal after the recovery (except for mild hepatomegaly with fatty infiltration). None of the patients has had a second episode, perhaps as a result of preventive measures to avoid prolonged fasting during ensuing intercurrent illnesses. Hepatomegaly was a consistent physical finding in all patients. Laboratory findings included hypoglycemia, acidosis with mild or no ketosis, elevation of liver function tests, and massive dicarboxylic aciduria. The clinical and laboratory findings may be confused with those of patients with defects in fatty acid metabolism (see Chapter 86.1). In contrast to the latter, blood concentrations of acylcarnitine conjugates are normal in patients with HMG-CoA synthase deficiency. Fasting of these patients has produced the abovementioned clinical and biochemical abnormalities.

**Treatment** consisted of provision of adequate calories and avoidance of prolonged periods of fasting. No dietary protein restriction was needed.

The condition is inherited as an autosomal recessive trait. The gene (HMGCS2) for this enzyme is located on chromosome 1p13-p12 and several disease-causing mutations have been identified. The condition should be considered in any child with fasting hypoglycemia and is perhaps more common than appreciated.

**3-HYDROXY-3-METHYLGLUTARIC ACIDURIA**

This condition is a result of a deficiency of HMG-CoA lyase (see Fig. 85-4). This enzyme catalyzes the conversion of HMG-CoA to acetocetate and is a rate-limiting enzyme for ketogenesis (see Fig. 85-7). Clinically, more than 60% of patients become symptomatic between 3 and 11 mo of age (infantile form), whereas approximately 30% develop symptoms in the first few days of life (neonatal form). One child remained asymptomatic until 15 yr of age (childhood form). Episodes of vomiting, severe hypoglycemia, hypotonia, acidosis with mild or no ketosis, and dehydration may rapidly lead to lethargy, ataxia, and coma. These episodes often occur during a catabolic state such as fasting or an intercurrent infection. Hepatomegaly is common. These manifestations may be mistaken for Reye syndrome or medium-chain acyl-CoA dehydrogenase deficiency. Patients are usually clinically asymptomatic between the attacks; 1 patient died of acute cardiomyopathy at age 7 mo during a febrile illness. Development is usually normal, but intellectual disability and seizures with abnormalities of white matter (shown by MRI) have been observed in patients with prolonged episodes of hypoglycemia. Laboratory findings include hypoglycemia, moderate to severe hyperammonemia, and acidosis. There is mild or no ketosis (see Fig. 85-7). Urinary excretion of 3-hydroxy-3-methylglutaric acid and other proximal intermediate metabolites of leucine catabolism (3-methylglutaconic acid and 3-hydroxyisovaleric acid) is markedly increased causing the urine to smell like cat urine. These organic acids are excreted in the urine as carnitine conjugates, resulting in secondary carnitine deficiency. Glutaric and adipic acids may also be increased in urine during acute attacks. Diagnosis may be confirmed by enzyme assay in cultured fibroblasts, leukocytes, or liver specimens or by identification of the mutant gene. Prenatal diagnosis is possible by the assay of the enzyme in cultured amniocytes or a chorionic villus biopsy or by DNA analysis.

Treatment of acute episodes includes hydration, infusion of glucose to control hypoglycemia, provision of adequate calories, and administration of bicarbonate to correct acidosis. Hyperammonemia should be treated promptly (see Chapter 85.12). Exchange transfusion and peritoneal dialysis may be required in patients with severe hyperammonemia. Restriction of protein and fat intake is recommended for long-term management. Oral administration of L-carnitine (50-100 mg/kg/24 hr) prevents secondary carnitine deficiency. Prolonged fasting should be avoided. One child died after routine immunization. The condition is inherited as an autosomal recessive trait. The gene (HNGCL) for HMG-CoA lyase resides on chromosome 1p36.11 and several disease-causing mutations have been identified in different families. The gene defect appears to be more common in the Arabic population, especially in Saudi Arabia.

**SUCCINYL COENZYME A:3-KETOACID COENZYME A TRANSFERASE (SCOT) DEFICIENCY**

This enzyme is necessary for the metabolism of ketone bodies (acetocetate and 3-hydroxybutyrate) in peripheral tissues (see Fig. 85-7). A deficiency of this enzyme results in the underutilization and accumulation of ketone bodies and ketoacidosis. Only a few patients with succinyl coenzyme A:3-ketoacid coenzyme A transferase deficiency have been reported to date; the condition may not be rare because many cases are, perhaps, undiagnosed.

The presentation is an acute episode of unexplained severe ketoacidosis in an infant who had been growing and developing normally. About half of the patients become symptomatic in the 1st wk of life, and all become symptomatic before 2 yr of age. The acute episode is often precipitated by an intercurrent infection or a catabolic state. Death may occur during these episodes. A chronic subclinical ketosis usually persists between the attacks. Development is usually normal.

Laboratory findings during the acute episode are nonspecific and include metabolic acidosis and ketonuria with high levels of acetocetate and 3-hydroxybutyrate in blood and urine. No other organic acids are found in the blood or in the urine. Blood glucose levels are usually normal, but hypoglycemia has been reported in 2 affected newborn infants with severe ketoacidosis. Plasma amino acids are usually normal. Diagnosis can be established by demonstrating a deficiency of enzyme activity in cultured fibroblasts or by DNA analysis.

Treatment of acute episodes consists of hydration, correction of acidosis, and the provision of a diet adequate in calories. Long-term treatment with a high-carbohydrate diet and avoidance of catabolic states is recommended. This condition should be considered in any infant with unexplained bouts of ketoacidosis. The condition is inherited as an autosomal recessive trait. The gene (OXCT1) for this enzyme is located on chromosome 5p13, and several disease-causing mutations have been found in different families.

**MEVALONIC ACIDURIA**

Mevalonic acid, an intermediate metabolite of cholesterol synthesis, is converted to 5-phosphomevalonic acid by the action of the enzyme mevalonate kinase (MVK) (see Fig. 85-7). Based on clinical manifestations and degree of enzyme deficiency, 2 forms of this condition have been recognized.

**Mevalonic Aciduria, Severe Form**

Clinical manifestations include intellectual disability, failure to thrive, growth retardation, hypotonia, ataxia, hepatosplenomegaly, cataracts, and facial dysmorphism (dolichocephaly, frontal bossing, low-set ears, downward slanting of the eyes, and long eyelashes). Recurrent crises, characterized by fever, vomiting, diarrhea, arthralgia, edema, lymphadenopathy, further enlargement of liver and spleen, and morbilliform rash have been observed in all patients. These episodes last 4-5 days and recur up to 25 times/yr. Death may occur during these crises.

Laboratory findings include marked elevation of mevalonic acid in urine; the concentration may be as high as 56,000 µmole/mole of creatinine (normal: <0.3). Plasma levels of mevalonic acid are also greatly increased (as high as 54 µmole/dL; normal: <0.004). This is the only abnormal organic acid found in these patients. The level of mevalonic acid tends to correlate with the severity of the condition and increases during crises. Serum cholesterol concentration is normal or mildly decreased. Serum concentration of creatine kinase is markedly increased. Sedimentation rate and serum leukotriene-4 are increased.
during the crises. Serial examination of the brain by MRI reveals progressive atrophy of the cerebellum.

Diagnosis may be confirmed by assay of MVK activity in lymphocytes or in cultured fibroblasts or by DNA analysis. The enzyme activity in this form of the condition is below the detection level. No effective therapy is available. Treatment with high doses of prednisone (2 mg/kg/24 hr) causes improvement of the acute crises. The condition is inherited as an autosomal recessive trait. Prenatal diagnosis is possible by measurement of mevalonic acid in the amniotic fluid, by assay of the enzyme activity in cultured amniocytes or chorionic villus samples or by demonstration of the mutant gene. The gene (MVK) for the enzyme is on chromosome 12q24.

Periodic Fever with Hyperimmunoglobulinemia D (Mevalonic Aciduria, Mild Form)

See Chapter 163.

Some mutations of mevalonic kinase gene (MVK) cause mild deficiencies of the enzyme and produce the clinical picture of periodic fever with hyperimmunoglobulinemia D. These patients have periodic bouts of fever associated with abdominal pain, vomiting, diarrhea, arthralgia, arthritis, hepatosplenomegaly, lymphadenopathy, and morbilliform rash (even petechiae and purpura), which usually start before 1 yr of age. The attacks can be produced by vaccination, minor trauma, or stress; usually occur every 1-2 mo; and last 2-7 days. Patients are free of symptoms between acute attacks. The diagnostic laboratory finding is elevation of serum immunoglobulin D (IgD); IgA is also elevated in 80% of patients. During acute attacks, leukocytosis, increased C-reactive protein, and mild mevalonic aciduria may be present. High concentrations of serum IgD differentiate this condition from familial Mediterranean fever.

Treatment

See Chapter 163.

PROPIONIC ACIDEMIA (PROPIONYL COENZYME A CARBOXYLASE DEFICIENCY)

Propionic acid is an intermediate metabolite of isoleucine, valine, threonine, methionine, odd-chain fatty acids, and cholesterol catabolism. It is normally carboxylated to methylmalonic acid by the mitochondrial enzyme propionyl CoA carboxylase, which requires biotin as a cofactor (see Fig. 85-4). The enzyme is composed of 2 nonidentical subunits, α and β. Biotin is bound to the α subunit.

Clinical findings are nonspecific. In the severe form of the condition, patients develop symptoms in the first few days or weeks of life. Poor feeding, vomiting, hypotonia, lethargy, dehydration, and clinical signs of severe ketoacidosis progress rapidly to coma and death. Seizures occur in approximately 30% of affected infants. If an infant survives the first attack, similar episodes may occur during an intercurrent infection or constipation or after ingestion of a high-protein diet. Moderate to severe intellectual disability and neurologic manifestations reflective of extrapyramidal (dystonia, choreoathetosis, tremor), and pyramidal (paraplegia) dysfunction are common sequelae in the older survivors. Neuroimaging shows these abnormalities, which usually occur after an episode of metabolic compensation, to be a result of damage to the basal ganglia, especially to the globus pallidus. This phenomenon has been referred to in the literature as metabolic stroke. This is the main cause of neurologic sequelae seen in the surviving affected children.

In the milder forms, the older infant may have intellectual disability without acute attacks of ketosis. Some affected children may have episodes of unexplained severe ketoacidosis separated by periods of seemingly normal health. Mass screening of newborn infants has identified milder forms of the condition; a few of these infants were completely asymptomatic at diagnosis. The severity of clinical manifestations may also be variable within a family; in 1 kindred, a brother was diagnosed at 5 yr of age whereas his 13 yr old sister, with the same level of enzyme deficiency, was asymptomatic.

Laboratory findings during the acute attack include severe metabolic acidosis with a large anion gap, ketosis, neutropenia, thrombocytopenia, and hypoglycemia. Moderate to severe hyperammonemia is common; plasma ammonia concentrations usually correlate with the severity of the disease. In contrast to other causes of hyperammonemia, plasma concentration of glutamine is within normal limits or even decreased. Presence of severe metabolic acidosis differentiates propionic acidemia from hyperammonemias caused by urea cycle defects. Measurement of plasma ammonia is especially helpful in planning therapeutic strategy during episodes of exacerbation in a patient whose diagnosis has been established. Pathogenesis of hyperammonemia is not well understood. Glycine concentration is elevated in all body fluids (blood, urine, and spinal fluid) in almost all patients. This is the result of inhibition of glycine cleavage enzyme (Fig. 85-8) in the liver. Glycine elevation has also been observed in patients with methylmalonic acidemia. These disorders were collectively referred to as ketotic hyperglycinemia in the past before the specific enzyme deficiencies were elucidated. A decrease in plasma levels of branched-chain amino acids (leucine, isoleucine, valine) is a common finding. Mild to moderate increase in blood concentrations of lactate and lysis may also be present in these patients. Concentrations of propionic acid and methylcitric acid (presumably made by the condensation of propionyl CoA with oxaloacetic acid) are markedly elevated in the plasma and urine of infants with propionic acidemia. 3-Hydroxypropionic acid, propionylglycine, and other intermediate metabolites of isoleucine catabolism, such as tiglic acid, tiglylglycine, and 2-methylacetoacetic acid, are also found in urine. Moderate elevations in blood levels of ammonia, glycine, and previously mentioned organic acids usually persist between the acute attacks. CT scan and MRI of the brain may reveal cerebrocerebral atrophy, demyelination, and abnormalities in the globus pallidus and basal ganglia as the evidence of a metabolic stroke in this condition (see above).

The diagnosis of propionic acidemia should be differentiated from multiple carboxylase deficiencies (see above and Fig. 85-6). Infants with the latter condition may have skin manifestations and excrete large amounts of lactic acid, 3-methylcrotonic acid, and 3-hydroxyisovaleric acid in addition to propionic acid. The presence of hyperammonemia may suggest a genetic defect in the urea cycle enzymes. Infants with defects in the urea cycle are usually not acidotic (see Fig. 85-1) and have elevated levels of plasma glutamate. Definitive diagnosis of propionic acidemia can be established by measuring the enzyme activity in leukocytes or cultured fibroblasts or by DNA analysis.

Treatment of acute attacks includes hydration, correction of acidosis, and amelioration of the catabolic state by provision of adequate calories through parenteral hyperalimentation. Minimal amounts of protein (0.25 g/kg/24 hr), preferably as a protein deficient in propionate precursors, should be provided in the hyperalimentation fluid very early in the course of treatment. To curtail the possible production of propionic acid by intestinal bacteria, sterilization of the intestinal tract flora by antibiotics (oral neomycin, or metronidazole) should be promptly initiated. Constipation should also be treated. Patients with propionic acidemia may develop carnitine deficiency, presumably as a result of urinary loss of propionylcarnitine formed from the accumulated organic acid. Administration of L-carnitine (50-100 mg/kg/24 hr orally or 10 mg/kg/24 hr intravenously) normalizes fatty acid oxidation and improves acidosis. In patients with concomitant hyperammonemia, measures to reduce blood ammonia should be employed (see Chapter 85.12). Very ill patients with severe acidosis and hyperammonemia require peritoneal dialysis or hemodialysis to remove ammonia and other toxic compounds rapidly and efficiently. Although no infant with true propionic acidemia has been found to be responsive to biotin, this compound should be administered (10 mg/24 hr orally) to all infants during the first attack and until the diagnosis is established.

Long-term treatment consists of a low-protein diet (1.0-1.5 g/kg/24 hr) and administration of L-carnitine (50-100 mg/kg/24 hr orally). Synthetic proteins deficient in propionate precursors (isoleucine, valine, methionine, and threonine) may be used to increase the amount of dietary protein (to 1.5-2.0 g/kg/24 hr) while causing minimal change in propionate production. Excessive supplementation with these proteins may cause a deficiency of the essential amino acids,
especially isoleucine (which may cause a condition resembling acrodermatitis enteropathica; see Chapter 671). To avoid this problem, natural proteins should comprise most of the dietary protein (50–75%). Some patients may require chronic alkaline therapy to correct chronic acidosis. The concentration of ammonia in the blood usually normalizes between attacks, and chronic treatment of hyperammonemia is not usually needed. Catabolic states that may trigger acute attacks (infections, constipation) should be treated promptly and aggressively. Close monitoring of blood pH, amino acids, urinary content of propionate and its metabolites, and growth parameters is necessary to ensure the proper balance of the diet and the success of therapy.

Long-term prognosis is guarded. Death may occur during an acute attack. Normal psychomotor development is possible, especially in the mild forms identified through screening programs; most children identified clinically manifest some degree of permanent neurodevelopmental deficit such as tremor, dystonia, chorea, and pyramidal signs despite adequate therapy. These neurologic findings may be sequelae of a metabolic stroke occurring during an acute decompensation (see above). Cardiomyopathy with potential progression to heart failure and death may develop in older affected children despite adequate metabolic control. Acute pancreatitis has also been reported in these patients.

Prenatal diagnosis is achieved by measuring the enzyme activity in cultured amniotic cells or in samples of uncultured chorionic villi, by measurement of methylcitrate in amniotic fluid, or by identification of the mutant gene.

The condition is inherited as an autosomal recessive trait and can be identified by mass screening of newborns with a worldwide prevalence of 1:50,000 to 1:100,000 live births. It is more prevalent in Saudi Arabia (1:2,000 to 1:5,000 live births). The gene for the α subunit (PCCA) is located on chromosome 13q32 and that of the β subunit (PCCB) is mapped to the chromosome 3q21-q22. Mutations in either gene can cause the condition. Many mutations in either gene have been identified in different patients. Pregnancy with normal outcome has been reported in affected females.

**METHYLMALONIC ACIDEMIA**

Methylmalonic acid, a structural isomer of succinic acid, is usually derived from propionic acid as part of the catabolic pathways of isoleucine, valine, threonine, methionine, cholesterol, and odd-chain fatty acids. Two enzymes are involved in the conversion of D-methylmalonic acid to succinic acid: methylmalonyl CoA racemase, which forms the 1. isomer; and methylmalonyl CoA mutase, which converts the 1.-methylmalonic acid to succinic acid (see Fig. 85-4). The latter enzyme requires adenosylcobalamin, a metabolite of vitamin B₁₂, as a coenzyme. Deficiency of either the mutase or its coenzyme causes the accumulation of methylmalonic acid and its precursors in body fluids. A deficiency of the racemase can be associated with mild elevations of methylmalonic acid, but the clinical consequence of racemase deficiency is not known.

At least 2 forms of mutase apoenzyme deficiencies have been identified. These are designated mut⁺, meaning no detectable enzyme activity, and mut⁻, indicating residual, although abnormal, mutase activity. The majority of reported patients with methylmalonic acidemia have a deficiency of the mutase apoenzyme (mut⁺ or mut⁻). These patients are not responsive to vitamin B₁₂ therapy. In the remaining patients with methylmalonic acidemia, the defect resides in the formation of adenosylcobalamin.

**Defects in Metabolism of Vitamin B₁₂ (Cobalamin)**

Dietary vitamin B₁₂ requires intrinsic factor, a glycoprotein secreted by the gastric parietal cells, for absorption in the terminal ileum. It is transported in the blood by haptocorrin and transcobalamin. The transcobalamin–cobalamin complex (TC-Cbl) is recognized by a specific receptor on the cell membrane and enters the cell by endocytosis. TC-Cbl is hydrolyzed in the lysosome, and free cobalamin is released into the cytosol (see Fig. 85-4). In the cytoplasm, cobalamin binds to the MMACHC protein (see chlC later), which reduces the cobalt of the molecule from 3 valences (cob[III]alamin) to 2 (cob[II]alamin) before it enters the mitochondria, where it reacts with adenosine triphosphate and an unknown reductase to form adenosylcobalamin (coenzyme for methylmalonyl CoA mutase). Alternatively, partially reduced cobalamin in the cytosol may interact with methionine synthase and methionine synthase reductase to form methylcobalamin (coenzyme for methionine synthase; see Fig. 85-3). The MMADHC protein (see chlD) appears to play a role in determining whether cobalamin enters the mitochondria or remains in the cytoplasm.

Uptake of TC-Cbl by cells is impaired in individuals with mutations affecting transcobalamin receptor which is located on the cell surface. Individuals homozygous for mutations at the CD320 gene, which encodes the transcobalamin receptor, have elevations of serum methylmalonic acid, which can be detected by newborn screening using tandem mass spectroscopy, but it is not clear whether there is a clinical phenotype associated with this disorder.

Nine different defects in the intracellular metabolism of cobalamin have been identified. These are designated chlA through chlG, chlI, and chlK (chl stands for a defect in any step of cobalamin metabolism). The chlA, chlB, and chlD variant defects cause methylmalonic acidemia alone. In patients with chlC, chlD, chlE, and chlF defects, synthesis of both adenosylcobalamin and methylcobalamin is impaired, causing homocystinuria in addition to methylmalonic acidemia. The chlD variant 1, chlE, and the chlG defects affect only the synthesis of methylcobalamin, resulting in homocystinuria without methylmalonic aciduria, but usually with megaloblastic anemia (see Chapter 85.3).

**Clinical manifestations** of patients with methylmalonic acidemia caused by mut⁰, mut⁺, chlA, chlB, and chlD variant 2 are similar. There are wide variations in clinical presentation, ranging from very sick newborn infants to asymptomatic adults, regardless of the nature of the enzymatic defect or the biochemical abnormalities. In severe forms, lethargy, feeding problems, vomiting, tachyypnea (from acidosis), and hypotonia may develop in the first few days of life and may progress to coma and death if untreated. Infants who survive the first attack may go on to develop similar acute metabolic episodes during a catabolic state (such as infection) or after ingestion of a high-protein diet. Between the acute attacks, the patient commonly continues to exhibit hypotonia and feeding problems with failure to thrive. In milder forms, patients may present later in life with hypotonia, failure to thrive, and developmental delay. Asymptomatic patients with typical biochemical abnormalities of methylmalonic acidemia are also reported. It is important to note that mental development and IQ of patients with methylmalonic acidemia may remain within the normal range despite repeated acute attacks and regardless of the nature of the enzyme deficiency. In a study of patients with different forms of the condition, developmental delay was noted in 47%. One adolescent girl with a mut⁻ deficiency had an IQ of 129.

The episodic nature of the condition and its biochemical abnormalities may be confused with those of ethylene glycol (antifreeze) ingestion. The peak of propionate in a blood sample from an infant with methylmalonic acidemia has been mistaken for ethylene glycol when the sample was assayed by gas chromatography without mass spectrometry.

**Laboratory findings** include ketosis, acidosis, anemia, neutropenia, thrombocytopenia, hyperglycinemia, hyperammonemia, hypoglycemia, and the presence of large quantities of methylmalonic acid in body fluids (see Fig. 85-6). Propionic acid and its metabolites 3-hydroxypropionate and methylcitrate are also found in the urine. Hyperammonemia may suggest the presence of genetic defects in the urea cycle enzymes; patients with defects in urea cycle enzymes are not acidic (see Fig. 85-12). The reason for hyperammonemia is not well understood.

**Diagnosis** can be confirmed by measuring propionate incorporation and performing complementation analysis in cultured fibroblasts, by measuring the specific activity of the mutase enzyme in biopsies or cell extracts or by identifying the mutations in the causal gene.

**Treatment** of acute attacks is similar to that of attacks in patients with propionic acidemia (see above), except that large doses (1 mg/24 hr) of vitamin B₁₂ are used instead of biotin. Long-term treatment consists of administration of a low-protein diet (1.0–1.5 g/
Glycine is a nonessential amino acid synthesized mainly from serine and threonine. Structurally, it is the simplest amino acid. It is involved in many reactions in the body, especially in the nervous system where it functions as a neurotransmitter (excitatory in the cortex, inhibitory in the brainstem and the spinal cord; see Chapter 85.11). Its main catalytic pathway requires the complex glycine cleavage enzyme to cleave the first carbon of glycine and convert it to carbon dioxide (see Fig. 85-8). The glycine cleavage protein, a mitochondrial multienzyme, is composed of 4 proteins: P protein (glycine decarboxylase), H protein, T protein, and L protein, which are encoded by 4 different genes.

85.7 Glycine
Iraj Rezvani

Glycine is synthesized mainly from serine and threonine. Structurally, it is the simplest amino acid. It is involved in many reactions in the body, especially in the nervous system where it functions as a neurotransmitter (excitatory in the cortex, inhibitory in the brainstem and the spinal cord; see Chapter 85.11). Its main catalytic pathway requires the complex glycine cleavage enzyme to cleave the first carbon of glycine and convert it to carbon dioxide (see Fig. 85-8). The glycine cleavage protein, a mitochondrial multienzyme, is composed of 4 proteins: P protein (glycine decarboxylase), H protein, T protein, and L protein, which are encoded by 4 different genes.
Neonatal Hyperglycemia
This is the most common form of NKH. Clinical manifestations develop in the first few days of life (between 6 hr and 8 days after birth). Poor feeding, failure to suck, lethargy, and profound hypotonia may progress rapidly to a deep coma, apnea, and death. Convulsions, especially myoclonic seizures and hiccups, are common.

Laboratory findings reveal moderate to severe hyperglycinemia (as high as 8 times normal) and hyperglycinuria. The unequivocal elevation of glycine concentration in the spinal fluid (15-30 times normal) and the high ratio of glycine concentration in spinal fluid to that in plasma (a value > 0.08) are diagnostic of NKH. Serum pH is normal; plasma serine levels are usually low.

Approximately 30% of affected infants die despite supportive therapy. Those who survive develop profound psychomotor retardation and intractable seizure disorders (myoclonic and/or grand mal seizures). Hydrocephalus, requiring shunting, and pulmonary hypertension have been noted in some survivors.

Infantile Nonketotic Hyperglycinemia
These previously normal infants develop signs and symptoms of neonatal NKH (see above) after 6 mo of age. Seizures are the common presenting signs. This condition appears to be a milder form of hyperglycinemia where the clinical presentation is delayed.
neonatal hyperglycinemia; infants usually survive and intellectual disability is not as profound as in the neonatal form.

**Laboratory findings** in these patients are identical to those seen in the neonatal form.

**Late-Onset Nonketotic Hyperglycinemia, Mild Episodic Form**

Progressive spastic diplegia, optic atrophy, and choreathetotic movements are the main clinical manifestations. Age of onset has been between 2 and 33 yr. Symptoms of delirium, chorea, and vertical gaze palsy may occur episodically in some patients during an intercurrent infection. Mental development is usually normal, but mild cognitive impairment has been reported in some patients. Seizures have been reported in only 1 patient.

**Laboratory findings** are similar to but not as pronounced as in the neonatal form.

**Transient Nonketotic Hyperglycinemia**

Most clinical and laboratory manifestations of this form are indistinguishable from those of the neonatal form. By 2-8 wk of age, however, the elevated glycine levels in plasma and CSF normalize and a complete clinical recovery may occur. Most of these patients develop normally with no neurologic sequelae, but intellectual disability has been noted in some. The etiology of this condition is not known, but it is believed to be a consequence of immaturity of the enzyme system.

All forms of NKH should be differentiated from ketotic hyperglycinemia, d-glyceric aciduria (see below), and ingestion of valproic acid. The latter compound causes a moderate increase in blood and urinary concentrations of glycine. Repeat assays after discontinuation of the drug should establish the diagnosis.

Diagnosis can be established by assay of the enzyme in liver or brain specimens or by identification of the mutation. Enzyme activity in the neonatal form is close to zero, whereas in the other forms, some residual activity is present. In most patients with the neonatal form, the enzyme defect resides in the P protein; defects in the T protein account for the rest. The enzyme assay in 3 patients with the infantile and late-onset forms has revealed 2 patients with a defect in the T protein and 1 with a defect in the H protein.

No effective treatment is known. Exchange transfusion, dietary restriction of glycine, and administration of sodium benzoate or folate have not altered the neurologic outcome. Drugs that counteract the effect of glycine on neuronal cells, such as strychnine, diazepam, and dextromethorphan, have shown some beneficial effects only in patients with the mild forms of the condition.

NKH is inherited as an autosomal recessive trait. The prevalence is not known, but high frequency of the disorder has been noted in northern Finland (1 in 12,000 live births). The newborn screening method using tandem mass spectrometry may not identify affected infants. The gene for P protein (GLDC) is on chromosome 9p24.1. The gene for H protein (GCH1) is mapped to chromosome 1q23.2 and that for T protein (AMT) is on chromosome 3p21.31. The L protein gene (DLD) is on chromosome 7q31.7. Several disease-causing mutations have been identified. Prenatal diagnosis has been accomplished by performing an assay of the enzyme activity in chorionic villous biopsy specimens or by identification of the mutant gene.

**SARCOSINEMIA**

Increased concentrations of sarcosine (N-methylglycine) are observed in both blood and urine, but no consistent clinical picture has been attributed to this metabolic defect. This is a recessively inherited metabolic condition caused by a defect in sarcosine dehydrogenase, the enzyme that converts sarcosine to glycine (see Fig. 85-8). The gene for this enzyme (SARDH) is on chromosome 9q34.2.

**D-GLYCERIC ACIDURIA**

D-Glyceric acid is an intermediate metabolite of serine and fructose metabolism. This rare condition is caused by deficiency of glyceraldehyde kinase enzyme (see Fig. 85-8). **Clinical manifestations** are highly variable. In the severe form of the condition, signs and symptoms of encephalopathy (hypotonia, seizures, and mental and motor deficits) with laboratory findings of hyperglycinemia and hyperglycinuria are suggestive of NKH. These patients have elevated levels of D-glyceric acid in all body fluids and excrete large quantities of D-glyceric acid in urine. This compound is not normally detectable in urine. Mild forms of the condition with mild speech delay or even normal development have also been reported.

No effective therapy is available. Restriction of fructose reduced the incidence of seizures in 1 patient. The gene for glyceraldehyde kinase (GLYCTK) is on chromosome 3p21.1.

**TRIMETHYLAMINURIA**

Trimethylamine is normally produced in the intestine from the breakdown of dietary choline and trimethylamine oxide by bacteria. Egg yolk and liver are the main sources of choline, and fish is the major source of trimethylamine oxide. Trimethylamine is absorbed and oxidized in the liver by trimethylamine oxidase (flavin-containing monoxygenases) to trimethylamine oxide, which is odorless and excreted in the urine (see Fig. 85-8). Deficiency of this enzyme results in massive excretion of trimethylamine in urine. There is a foul body odor that resembles that of a rotten fish, which may have significant social and psychosocial ramifications. Transient symptomatic trimethylaminuria can occur in normal individuals following ingestion of large quantities of the abovementioned foods. Restriction of fish, eggs, liver, and other sources of choline (such as nuts and grains) in the diet significantly reduces the odor. Treatment with short courses of oral metronidazole, neomycin, or lactulose cause temporary reduction in the body odor. The gene for trimethylamine oxidase (EMO3) has been mapped to chromosome 1q24.3.

**HYPEROXALURIA AND OXALOSIS**

Normally, oxalic acid is derived mostly from oxidation of glyoxylic acid and, to a lesser degree, from oxidation of ascorbic acid (see Fig. 85-8). Glyoxylic acid is formed from oxidation of glycolic acid and glycine in the peroxisomes, and catabolism of hydroxyproline in the mitochondria (Figs. 85-8 and 85-9). Vegetables and foods containing oxalic acid, such as spinach and rhubarb, are the main exogenous sources of glycolic and oxalic acids; most of glyoxylic and oxalic acids are produced endogenously. Normally, a major portion of glyoxylic acid produced in the body is shuttled to peroxisomes where it is converted to glycine by the action of the enzyme alanine-glyoxylate aminotransferase. Deficiency of this enzyme causes hyperoxaluria type 1. Most of the remaining glyoxylate in the cytosol is reduced to glycolate by the action of the enzyme glyoxylate reductase/ hydroxypyruvate reductase. Deficiency of this enzyme causes hyperoxaluria type 2. These 2 pathways protect the body from excessive production of oxalic acid (see Fig. 85-8). Any glyoxylate that cannot be disposed of through these pathways is readily converted to oxalic acid by the action of the enzyme lactate dehydrogenase (LDH). Oxalic acid cannot be further metabolized in humans and is excreted in the urine as oxalates. Calcium oxalate is relatively insoluble in water and precipitates in tissues (kidneys and joints) if its concentration increases in the body.

**Secondary hyperoxaluria** has been observed in pyridoxine deficiency (cofactor for alanine-glyoxylate aminotransferase; see Fig. 85-8), in patients with inflammatory bowel disease, extensive resection of small bowel, or jejunointestinal bypass (enteric hyperoxaluria), after ingestion of ethylene glycol or high doses of vitamin C, and after administration of the anesthetic agent methoxylflurane (which oxidizes directly to oxalic acid). Acute, fatal hyperoxaluria may develop after ingestion of plants with high oxalic acid content such as sorrel or intentional ingestion of oxalic acid. Precipitation of calcium oxalate in tissues causes hypocalcemia, liver necrosis, renal failure, cardiac arrhythmia, and death. The lethal dose of oxalic acid is estimated to be between 5 and 30 g.

**Primary hyperoxaluria** is a genetic disorder in which large amounts of oxalates accumulate in the body. Three types of primary hyperoxaluria have been identified to date. The term oxalosis refers to deposition of calcium oxalate in parenchymal tissues.
Primary Hyperoxaluria Type 1
This rare condition is the most common form of primary hyperoxaluria. It is caused by deficiency of the peroxisomal enzyme alanine-glyoxylate aminotransferase, which is expressed only in the liver peroxisomes and requires pyridoxine (vitamin B<sub>6</sub>) as its cofactor. In the absence of this enzyme, glyoxylate, which cannot be converted to glycine, is transferred to the cytosol, where it is oxidized to oxalic acid (see above and Fig. 85-8).

There is a wide variation in the age of presentation (4 mo to 25 yr). The majority of patients become symptomatic in late childhood or early adolescence. In 19% of cases, symptoms develop before 1 yr of age (neonatal oxaluria). The initial clinical manifestations are related to renal stones and nephrocalcinosis. Renal colic and asymptomatic hematuria lead to a gradual deterioration of renal function, manifested by growth retardation and uremia. Most patients die before 20 yr of age from renal failure if the disorder is left untreated. Acute arthritis is a rare manifestation and may be misdiagnosed as gout because uric acid is usually elevated in patients with type 1 hyperoxaluria. Late forms of the disease presenting during adulthood have also been reported. Crystalline retinopathy and optic neuropathy causing visual loss have occurred in a few patients.

A marked increase in urinary excretion of oxalate (normal excretion 10-50 mg/24 hr) is the most important laboratory finding. The presence of oxalate crystals in urinary sediment is rarely helpful for diagnosis because such crystals are often seen in normal individuals. Urinary excretion of glycolic acid and glyoxylic acid is increased in most patients but not in all. Diagnosis can be confirmed by performing an assay of the enzyme in liver specimens or by identification of the mutant gene.

Treatment has been largely unsuccessful. In some patients (especially those whose condition is a result of mistargeting of the enzyme to the mitochondria; see below) administration of large doses of pyridoxine reduces urinary excretion of oxalate. Renal transplantation in patients with renal failure has not improved the outcome in most cases, because oxalosis has recurred in the transplanted kidney. Combined liver and kidney transplants have resulted in a significant decrease in plasma and urinary oxalate, and this may be the most effective treatment of this disorder, particularly in children.

The condition is inherited as an autosomal recessive trait. The gene for this enzyme (AGXT) is mapped to chromosome 2q37.3. Several mutations of the gene have been described in patients with this condition. The most common mutation results in the mistargeting of the enzyme to the mitochondria instead of the peroxisomes. In vitro enzyme activity in these patients may reach the level found in obligate heterozygotes. In vivo function remains defective, however. Approximately 30% of patients with hyperoxaluria type 1 are estimated to have this defect.

Prenatal diagnosis has been achieved by the measurement of fetal hepatic enzyme activity obtained by needle biopsy or by DNA analysis of chorionic villous villous samples.

Primary Hyperoxaluria Type 2
(L-Glyceric Aciduria)
This rare condition is caused by a deficiency of D-glycerate dehydrogenase glyoxylate reductase/hydroxypruvate reductase enzyme complex (see Fig. 85-8). A deficiency in the activity of this enzyme results in an accumulation of 2 intermediate metabolites, hydroxypruvate (the ketoacid of serine) and glyoxylic acid. Both these compounds are further metabolized by LDH to L-glyceraldehyde and oxalic acid, respectively. Approximately 30% of reported patients are from the Saulteaux-Ojibway Indians of Manitoba.

These patients are indistinguishable from those with hyperoxaluria type 1. Renal stones presenting with renal colic and hematuria may develop before age 2 yr. Renal failure is less common in this condition than in hyperoxaluria type 1; the urine contains large amounts of L-glyceraldehyde in addition to high levels of oxalate. L-Glyceraldehyde is not normally present in urine. Urinary excretion of glycolic acid and glyoxylic acid is not increased. The presence of L-glyceraldehyde without increased levels of glycolic and glyoxylic acids in urine differentiate this type from type 1 hyperoxaluria. Diagnosis can be confirmed by the enzyme assay in liver biopsy or by the identification of the mutant gene. The gene (GRHPR) is mapped to chromosome 9p13.2.

No effective therapy is available. As with the hyperoxaluria type 1 renal transplant does offer a cure because of recurrence of oxalosis in the transplanted kidney; no experience with kidney-liver transplantation is available at this time.

Primary Hyperoxaluria Type 3
Approximately 5% of patients with primary hyperoxaluria have neither type 1 nor type 2 hyperoxaluria. Genetic studies reveal mutations in the gene for 4-hydroxy-2-oxoglutarate aldolase enzyme. This mitochondrial enzyme catalyzes the final step in metabolic pathway of hydroxyproline generating pyruvate and glyoxylate from 4-hydroxy-2-oxoglutarate (HOG; see Figs. 85-8 and 85-9). In vitro studies show inhibition of glyoxylate reductase/hydroxypruvate reductase enzyme activity by high concentration of HOG (the compound that
Creatine Deficiency

Creatine is synthesized mainly in the liver, pancreas, and kidneys and to a lesser degree in the brain from arginine and glycine (Fig. 85-10) and is transported to muscles and the brain, where there is high activity of the enzyme creatine kinase. Phosphorylation and dephosphorylation of creatine in conjunction with adenosine triphosphate and generation of high-energy phosphate transfer reactions in these organs. Creatine is nonenzymatically metabolized to creatinine at a constant daily rate and is excreted in the urine. Three genetic conditions are known to cause creatine deficiency in the brain and other tissues. Two are because of deficiency of the enzymes involved in the biosynthesis of creatine. These enzymes are arginine:glycine amidinotransferase (AGAT) and guanidinoacetate methyltransferase (GAMT; Fig. 85-10). Both conditions respond well to creatine supplementation. The third condition, an X-linked inherited defect, is caused by deficiency of the creatine transporter (CRTR) protein and is not responsive to creatine administration.

Clinical manifestations of the 3 defects, which are similar, relate to the brain and muscles, and may appear in the first few weeks or months of life. Developmental delay, intellectual disability, speech delay, psychiatric symptoms (autistic behavior, hallucination), hypotonia, ataxia, and seizures are common findings. Dystonic movements are seen in severe GAMT deficiency.

Laboratory findings include decreased creatine and creatinine in blood and urine in patients with AGAT and GAMT defects. The urinary ratio of creatine to creatinine is increased in patients with a CRTR defect. Marked elevations of guanidinoacetate in blood, urine, and especially in spinal fluid (CSF), are diagnostic of GAMT defects. In contrast, low levels of guanidinoacetate are found in body fluids in the AGAT defect. Absence of creatine and creatine phosphate (in all 3 defects) and high levels of guanidinoacetate (in the GAMT defect) can be demonstrated in the brain by magnetic resonance spectroscopy (MRS). MRI of the brain shows signal hyperintensity in the globus pallidus. Diagnosis of AGAT or GAMT defects may be confirmed by measurement of the enzyme in the liver, cultured fibroblasts, or stimulated lymphoblasts or by the identification of the mutant gene DNA analysis of the gene. Diagnosis of CRTR is confirmed by DNA analysis or creatine uptake by fibroblasts.

Treatment with creatine monohydrate (350 mg-2 g/kg/day) orally results in a dramatic improvement in muscle tone and overall mental development and normalizes MRI and electroencephalographic findings in patients with AGAT and GAMT defects. It is believed that early treatment may assure normal development. No therapy is available for the CRTR defect; administration of creatine and its precursors (arginine and glycine) has failed to change the clinical course of the condition in affected patients. AGAT and GAMT defects are inherited as autosomal recessive traits. The gene for AGAT (GATM) is on chromosome 15q21.1 and that for GAMT (GAMT) is on chromosome 19p13.3. CRTR is an X-linked trait and the gene (SLC6A8) is on Xq28. CRTR defect is the most common cause of creatine deficiency, accounting for up to 1% of males with intellectual disability of unknown cause. AGAT defect is very rare (only 7 patients reported to date). Creatine deficiency must be considered in any patient with concomitant brain and muscle dysfunction, as treatment can produce a dramatic response in some cases.

Bibliography is available at Expert Consult.

85.8 Serine

Serine is a nonessential amino acid supplied through dietary sources and through its endogenous synthesis, mainly from glucose and glycine (see Fig. 85-10). The endogenous production of serine comprises an
Bibliography
important portion of the daily requirement of this amino acid, especially in the synaptic junctions where it functions as a neurotransmitter (see Chapter 85.11). Consequently, deficiency of any of the enzymes involved in the biosynthesis of serine causes neurologic manifestations. Affected patients respond favorably to oral supplementation with serine and glycine provided that the treatment is initiated very early in life. Figure 85-8 shows the metabolic pathway for synthesis and catabolism of serine.

**3-PHOSPHOGLYCERATE DEHYDROGENASE DEFICIENCY**

Deficiency of this enzyme causes deficiencies of serine and glycine in the body. Three forms of the condition have been recognized: infantile, juvenile, and adult forms. In the infantile form, which is the most common phenotype, the clinical manifestations appear typically in utero with microcephaly and intrauterine growth retardation. In 1 infant who was normocephalic at birth, the head failed to grow normally postnatally. Feeding problems, failure to thrive, vomiting, irritability, intractable seizures, severe developmental delay, and hypertonia progressing into spastic tetraplegia are common findings that develop shortly after birth. Nystagmus, cataracts, hypogonadism, and megaloblastic anemia have been observed in some affected infants.

**Laboratory findings** include low levels of serine and glycine in plasma and very low levels of serine and glycine in CSF. No abnormal organic acid metabolite is found in the urine. MRI of the brain shows cerebral atrophy with enlarged ventricles, significant attenuation of white matter and impaired myelinization.

The juvenile form of the condition has been reported in 2 siblings who presented at 5 and 9 yr of age with mild intellectual disability and absence seizures. Head size and MRI of the brain were normal.

Only 1 adult patient with congenital cataracts and intellectual disability has been reported. This patient developed progressive polyneuropathy resembling Charcot-Marie-Tooth disease type 2.

**Diagnosis** can be confirmed by measurement of the enzyme activity in cultured fibroblasts and by DNA analysis.

**Treatment** with high doses of serine (500-700 mg/kg/24 hr, orally) alone or in conjunction with glycine (200-300 mg/kg/24 hr) normalizes the serine levels in the blood and CSF. This treatment produces significant improvement in all clinical findings except for the psychomotor retardation; seizure activity subsides within a few days of therapy and may be halted completely. Microcephaly improves in young affected infants. There is evidence to indicate that psychomotor retardation may be prevented if the treatment starts in the first few days of life or, even better, in utero.

The condition is inherited as an autosomal recessive trait. The gene for 3-phosphoglycerate dehydrogenase enzyme (PHGDH) has been mapped to chromosome 1p12 and a few disease-producing mutations have been identified in different families. Prenatal diagnosis has been achieved by DNA analysis in a family with previously affected offspring; administration of serine to the mother corrected the microcephaly in the affected fetus as evidenced by ultrasound imaging.

**PHOSPHOSERINE AMINOTRANSFERASE DEFICIENCY**

This enzyme catalyzes conversion of 3-phosphohydroxypruvate to 3-phosphoserine (see Fig. 85-10). Deficiency of this enzyme has been reported in 2 siblings from an English family. Poor feeding, cyanotic episodes, and jerky movements developed shortly after birth in the first affected infant and progressed to intractable seizures by 9 wk of age. The infant was microcephalic. Electroencephalography (EEG) was consistent with multifocal seizures. Neuroimaging showed generalized cerebral and cerebellar atrophies. Laboratory studies were all within normal limits except for a mild decrease in plasma levels of serine and glycine with pronounced deficiencies of these 2 amino acids in the CSF.

**Treatment** with serine (500 mg/kg/day) and glycine (200 mg/kg/day) was started at 11 wk of age but resulted in only marginal clinical improvement; the child died at 7 mo of age. The younger affected sibling, who was treated with serine and glycine within a few hours after birth, remained asymptomatic at 3 yr of age.

The condition is inherited as an autosomal recessive trait and the gene for the enzyme (PSAT1) is mapped to chromosome 9q21.2. Based on this single report one can assume that this is a treatable genetic condition with a favorable outcome if the treatment is initiated early in life.

**Bibliography is available at Expert Consult.**

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**85.9 Proline**

*Iraj Rezvani*

Proline is a nonessential amino acid synthesized endogenously from glutamic acid, ornithine, and arginine (see Fig. 85-9). Proline and hydroxyproline are found in high concentrations in collagen. Neither of these amino acids is normally found in urine in the free form except in early infancy. Excretion of proline and hydroxyproline as iminopeptides (dipeptides and tripeptides containing proline or hydroxyproline) reflects collagen turnover and is increased in disorders of accelerated collagen turnover, such as rickets or hyperparathyroidism. Proline is also found at synaptic junctions and functions as a neurotransmitter (see Chapter 85.11). The catabolic pathway of proline/hydroxyproline produces glyoxylic acid which can be further metabolized to glycine or oxalic acid (see Fig. 85-8).

**HYPERPROLINEMIA**

Two types of primary hyperprolinemia have been described.

**Hyperprolinemia Type I**

This rare autosomal recessive condition is caused by deficiency of proline oxidase (proline dehydrogenase; see Fig. 85-9). Clinical manifestations are variable; some affected individuals are asymptomatic but patients with severe psychomotor retardation and seizures have been reported. Schizophrenia is a common finding in these patients. The gene for proline oxidase (PRODH) is located on chromosome 22q11.2 and several disease-causing mutations have been identified. Microdeletions involving this region of chromosome 22 cause velocardiofacial (DiGeorge, Shprintzen) syndrome; approximately 50% of patients with this syndrome have been reported to have hyperprolinemia type I. Therefore, all patients with hyperprolinemia type I should be screened (by fluorescence in situ hybridization analysis) for presence of DiGeorge syndrome.

**Laboratory studies** reveal high concentrations of proline in plasma, urine, and in the CSF. Approximately 30% of obligate heterozygous individuals (parents, siblings) also have hyperprolinemia. Increased urinary excretion of hydroxyproline and glycine is also present; this is from saturation of the shared tubular reabsorption mechanism by massive prolinuria.

No effective treatment has yet emerged. Restriction of dietary proline causes modest improvement in plasma proline with no proven clinical benefit.

**Hyperprolinemia Type II**

This is a rare autosomal recessive condition caused by the deficiency of pyrroline-carboxylic acid dehydrogenase (aldehyde dehydrogenase 4 [ALDH4]; see Fig. 85-9). Psychomotor retardation (modest to severe) and seizures (usually precipitated by an intercurrent infection) have been reported in most affected children, but asymptomatic patients have also been reported.

**Laboratory studies** reveal increased concentrations of proline and Δ¹-pyrrolino-5-carboxylic acid (PSC) in blood, urine, and the CSF.
**Bibliography**


Increased excretion of xanthurenic acid also has been reported in this condition. The presence of PSC differentiates this condition from hyperprolinemia type I (see above). Increased levels of PSC in body fluids, especially in the CNS, cause inactivation of vitamin B6, and generate a state of vitamin B6 dependency (see Chapter 85.14). Vitamin B6 dependency is perhaps the main cause of seizures and neurologic findings in this condition and may explain the variability in clinical manifestations in different patients. Treatment with high doses of vitamin B6 in conjunction with a diet low in proline is recommended but the experience remains very limited because of paucity of patients.

The gene for P5C dehydrogenase (ALDH4) is on chromosome 1p36.13. Oral supplementation with proline, ascorbic acid, and manganese, and the topical use of proline and glycine, result in an improvement in leg ulcers. These treatments have not been found to be consistently effective in all patients.

The gene for prolidase enzyme (PEPD) has been mapped to chromosome 19q13.11 and several disease-causing mutations have been identified in different families.

Bibliography is available at Expert Consult.

### 85.10 Glutamic Acid

Iraj Rezvani

Glutamic acid and its aminated derivative glutamine have a wide range of functions in the body. One of the major products of glutamic acid is glutathione (γ-glutamyl cysteinylglycine). This ubiquitous tripeptide, with its function as the major antioxidant in the body, is synthesized and degraded through a complex cycle called the γ-glutamyl cycle (Fig. 85-11). Because of its free sulfhydryl (-SH) group and its abundance in the cell, glutathione protects other sulfhydryl-containing compounds (such as enzymes and CoA) from oxidation. It is also involved in the detoxification of peroxides, including hydrogen peroxide, and in keeping the intracellular milieu in a reduced state. The common consequences of glutathione deficiency are hemolysis and hemolytic anemia. In addition, glutathione participates in amino acid transport...
**Bibliography**


across the cell membrane through the γ-glutamyl cycle. Glutamic acid is also the precursor of γ-aminobutyric acid (GABA), a major neurotransmitter in the nervous system (see Chapter 85.11).

GLUTATHIONE SYNTHETASE DEFICIENCY
See Figure 85-11.

Three forms of this rare condition have been reported. In the severe form, which is a result of generalized deficiency of the enzyme, severe acidosis and massive 5-oxoprolinuria are the rule. In the mild form, in which the enzyme deficiency causes glutathione deficiency only in erythrocytes, neither 5-oxoprolinuria nor acidosis has been observed. A moderate form has also been observed in which the hemolytic anemia is associated with variable degrees of acidosis and 5-oxoprolinuria. In all forms, patients have hemolytic anemia secondary to glutathione deficiency.

Glutathione Synthetase Deficiency, Severe Form (Pyroglutamic Acidemia, Severe 5-Oxoprolinuria) and Moderate Form
Affected newborn infants with this rare condition usually develop acute symptoms of metabolic acidosis, jaundice, and mild to moderate hemolytic anemia in the first few days of life. Chronic acidosis continues after recovery. Similar episodes of life-threatening acidosis may occur during an infection such as gastroenteritis or after a surgical procedure. Progressive neurologic damage, manifested by intellectual disability, spastic tetraparesis, ataxia, tremor, dysarthria, and seizures, develops with age. Susceptibility to infection, presumably as a consequence of granulocyte dysfunction, is observed in some patients. Patients with the moderate form of the condition have milder acidosis and less 5-oxoprolinuria than is seen in the severe form, with no neuromategicologic signs.

Laboratory findings include metabolic acidosis, mild to moderate degrees of hemolytic anemia, and 5-oxoprolinuria. High concentrations of 5-oxoprolin are also found in blood. The urinary and blood levels of 5-oxoprolin are less pronounced in patients with moderate form of the condition. The glutathione content of erythrocytes is markedly decreased. Increased synthesis of 5-oxoprolin in this disorder is believed to be a result of the conversion of γ-glutamylcysteine to 5-oxoprolin by the enzyme γ-glutamyl cyclotransferase (see Fig. 85-11). γ-Glutamylcysteine production increases greatly because the normal inhibitory effect of glutathione on the γ-glutamylcysteine synthetase enzyme is removed. A deficiency of glutathione synthetase has been demonstrated in a variety of cells including erythrocytes.

Treatment of acute attack includes hydration, correction of acidosis (by infusion of sodium bicarbonate), and measures to correct anemia and hyperbilirubinemia. Chronic administration of alkalis is usually needed indefinitely. Administration of large doses of vitamins C and E has been recommended. Drugs and oxidants that are known to cause hemolysis and stressful catabolic states should be avoided. Oral administration of glutathione analogs has been tried with variable success.

Prenatal diagnosis can be achieved by the measurement of 5-oxoprolin in amniotic fluid, by enzyme analysis in cultured amniocytes or chronic villous samples, or by DNA analysis of the gene. Successful pregnancy in an affected female (moderate form), with favorable outcomes for both mother and infant, has been reported.

Glutathione Synthetase Deficiency, Mild Form
This form has been reported in only a few patients. Mild to moderate hemolytic anemia has been the only clinical finding in these patients. Splenomegaly has been reported in some patients. Cognitive development is normal; metabolic acidosis and increased concentrations of 5-oxoprolin do not occur. Similar to other types of glutathione synthetase deficiency, this form is caused by mutations in the gene that encodes the enzyme. These mutations, however, decrease the half-life of the enzyme, which causes an increased rate of protein turnover without affecting its catalytic function. The expedited rate of enzyme turnover caused by these mutations is of no consequence for tissues with protein synthetic capability. However, inability of mature erythrocytes to synthesize protein, results in glutathione deficiency in the erythrocytes. Treatment is that of hemolytic anemia and avoidance of drugs and oxidants that can trigger the hemolytic process.

All forms of the condition are inherited as an autosomal recessive trait. The gene for this enzyme (GSSD) is located on chromosome 20q11.2. Several disease-causing mutations have been identified in different families.

5-Oxoprolinase Deficiency (5-Oxoprolinuria)
The main cause of massive 5-oxoprolinuria is glutathione synthetase deficiency (see above). Moderate 5-oxoprolinuria has been found in a variety of metabolic and acquired conditions, such as in patients with severe burns, Stevens-Johnson syndrome, homocystinuria, urea cycle defects, and tyrosinemia type I.

A few individuals with moderate 5-oxoprolinuria (4-10 g/day) as a result of 5-oxoprolinase (see Fig. 85-11) deficiency have been identified. No specific clinical picture has yet emerged; completely asymptomatic affected individuals have also been identified. It is, therefore, not clear whether 5-oxoprolinase deficiency is of any clinical consequence. No treatment has been recommended. The gene for the enzyme (OPLAH) is on chromosome 8q24.3.

Glutathione Synthetase Deficiency, Severe Form (Pyroglutamic Acidemia, Severe 5-Oxoprolinuria) and Moderate Form

5-Oxoprolinase Deficiency (5-Oxoprolinuria)

γ-Glutamylcysteine Synthetase Deficiency
Only a few patients with this enzyme deficiency have been reported. The most consistent clinical manifestation has been mild chronic hemolytic anemia. Acute attacks of hemolysis have occurred after exposure to sulfonamides. Peripheral neuropathy and progressive spino-cerebellar degeneration have been noted in 2 siblings in adulthood. Laboratory findings of chronic hemolytic anemia were present in all patients. Generalized aminoaciduria is also present because the γ-glutamyl cycle is involved in amino acid transport in cells (see Fig. 85-11). Treatment is that of hemolytic anemia and avoidance of drugs and oxidants that may trigger the hemolytic process. The condition is inherited as an autosomal recessive trait; the gene (GCLC) is mapped to chromosome 6p12.1.

GLUTATHIONEMIA (γ-GLUTAMYL TRANSPEPTIDASE DEFICIENCY)
This enzyme is present in any cell that has secretory or absorptive functions. It is especially abundant in the kidneys, pancreas, intestines, and liver. The enzyme is also present in the bile. Measurement of this enzyme in the blood is commonly performed to evaluate liver and bile duct diseases.

Deficiency of this enzyme causes elevation in glutathione concentrations in body fluids, but the cellular levels remain normal (see Fig. 85-11). Because only a few patients with enzyme deficiency have been reported, the scope of clinical manifestations has not yet been defined. Mild to moderate intellectual disability and severe behavioral problems were observed in 3 patients. One of the 2 sisters with this condition had normal intelligence as an adult, however, and the other had Prader-Willi syndrome.

Laboratory findings include marked elevations in urinary concentrations of glutathione (up to 1 g/day), γ-glutamylcysteine, and cysteine. None of the reported patients has had generalized aminoaciduria, a finding that would have been expected to occur in this enzyme deficiency (see Fig. 85-11).

Diagnosis can be confirmed by measurement of the enzyme activity in leukocytes or cultured skin fibroblasts. No effective treatment is available.

The condition is inherited as an autosomal recessive trait. The enzyme GGT (γ-glutamyl transpeptidase) is a complex protein and is encoded by at least 7 genes.

GENETIC DISORDERS OF METABOLISM OF γ-AMINOBUTYRIC ACID
See also Chapter 85.11.

Congenital Glutamine Deficiency
Glutamine is synthesized endogenously from glutamate and ammonia by a ubiquitous enzyme, glutamine synthetase (see Fig. 85-11).
Glutamine is known to be involved in several important functions, including detoxification of ammonia. Deficiency of this enzyme, resulting in glutamine deficiency, has been reported in 3 infants from 3 unrelated families. All affected infants manifested multiorgan involvement including significant brain malformations (abnormal gyrations, hypomyelination), facial abnormalities (broad nasal root, low-set ears) hypotonia and seizures at birth. Two of the patients died from multigorgan failure (respiratory and heart failure) in the neonatal period; 1 child was alive at 3 yr of age with severe developmental delay. Glutamine was absent in plasma, urine, and CSF; but plasma levels of glutamic acid were normal. Genetic defects of this enzyme underline the critical role of glutamine in embryogenesis especially in normal brain development. The condition is inherited as an autosomal recessive trait; the gene for glutamine synthetase (GLUL) is mapped to chromosome 1q25.3

Bibliography is available at Expert Consult.

### 85.11 Genetic Disorders of Neurotransmitters

Iraj Rezvani and K. Michael Gibson

Neurotransmitters are chemical substances released from the axonal end of excited neurons at the synaptic junctions; they mediate initiation and amplification or inhibition of neural impulses. A number of amino acids and their metabolites comprise the bulk of neurotransmitters. Mutations in genes responsible for the synthesis or degradation of these substances may cause conditions that usually manifest neurologic and/or psychiatric abnormalities (Table 85-2). In the past, children affected by disorders of neurotransmitters have been given diagnoses such as cerebral palsy, seizure disorder, parkinsonism, dystonia, or autism. Diagnosis, in most cases, requires specialized laboratory studies of the CSF, because some of the neurotransmitters generated in the CNS (dopamine and serotonin) do not cross the blood–brain barrier and their abnormal concentrations are not detected in the serum or urine. An ever-growing number of these conditions are being identified; diseases that were once thought to be very rare are now diagnosed with increasing frequency.

#### Table 85-2 Genetic Disorders of Neurotransmitters in Children

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AADC, aromatic l-amino acid decarboxylase; BH4, tetrahydrobiopterin; DAT, dopamine transporter; DβH, dopamine β-hydroxylase; GABA, γ-aminobutyric acid; GHB, γ-hydroxybutyric; HDC, histidine decarboxylase; hyperphe, hyperphenylalaninemia; MAO, monoamine oxidase; NKH, nonketotic hyperglycinemia; 3-PGD, 3-phosphoglycerate dehydrogenase; PSAT, phosphoserine aminotransferase; TH, tyrosine hydroxylase; VMAT2, vesicular monoamine transporter 2.

**TYROSINE HYDROXYLASE DEFICIENCY (INFANTILE PARKINSONISM, AUTOSOMAL RECESSIVE DOPA-RESPONSIVE DYSTONIA, SEGAWA SYNDROME, AUTOSOMAL RECESSIVE FORM)**

Tyrosine hydroxylase catalyzes the formation of l-dopa from tyrosine. Deficiency of this enzyme, reported in several children, results in deficiencies of dopamine and norepinephrine (see Fig. 85-2). The clinical picture resembles that of autosomal dominant dystonia caused by GTP cyclohydrase deficiency (see below); the clinical spectrum of the condition is still being elucidated.

**Clinical manifestations** range from mild to very severe. In general, 2 phenotypes have been recognized. In the mild form (dopa-responsive dystonia or type A), symptoms of unilateral limb dystonia causing gait incoordination and postural tremor occur in childhood and worsen with age if the condition remains untreated. Diurnal variation of symptoms (worse at the end of the day) may be present. Cognitive development is usually normal. In the severe form of the condition (infantile parkinsonism, infantile encephalopathy or type B), the clinical manifestations occur at birth or shortly thereafter. These include microcephaly, developmental delay, involuntary movements of the limbs with spasticity, dystonia, ptosis, expressionless face, oculogyric crises (upward rolling-eye movements) and autonomic dysfunction (temperature instability, excessive sweating, hypoglycemia, salivation, tremor, gastrointestinal reflux, constipation). Brisk reflexes, myoclonus, athetosis and distal chorea may be present. This form usually does not respond to treatment with l-dopa.

**Laboratory findings** include reduced levels of dopamine and its metabolite homovanillic acid (HVA), and normal concentrations of BH4, neopterin, and 5-hydroxyindoleacetic acid (5-HIAA, a metabolite of serotonin) in the CSF. Serum prolactin levels are usually elevated. These findings are not diagnostic of the condition; diagnosis should be established by gene study.

**Treatment** with l-dopa/carbidopa results in significant clinical improvement in most patients, but is invariably associated with l-dopa induced dyskinesias. To minimize the side effects of therapy, the treatment should be started with a low dose and increased very slowly if needed. Other therapeutic interventions include anticholinergics, serotonergic agents and monoamine oxidase (MAO) B inhibitors, including amantadine, biperiden, and selegeline. Bilateral subthalamic nucleus deep brain stimulation has shown clinical efficacy in 1 case. The gene for tyrosine hydroxylase (TH) is located on chromosome 11p15.5; it is inherited as an autosomal-recessive trait.
Bibliography
Aromatic L-Amino Acid Decarboxylase Deficiency

Aromatic L-amino acid decarboxylase (AADC) catalyzes the decarboxylation of both 5-hydroxytryptophan (to form serotonin, see Fig. 85-5) and L-dopa (to generate dopamine, see Fig. 85-2). Clinical manifestations are related to underproduction of dopamine and serotonin. Poor feeding, lethargy, hypotension, hypothermia, eye rolling (oculogyric crises), and ptosis have been observed in affected neonates. Clinical findings in infants and older children include developmental delay, truncal hypotonia with hypertonia of limbs, oculogyric crises, extra-pyramidal movements (choreathetosis, dystonia, myoclonus), and autonomic abnormalities (sweating, salivation, irritability, temperature instability, hypotension). Symptoms often have a diurnal variation becoming worse by the end of the day.

Laboratory findings include decreased concentrations of dopamine and serotonin and their metabolites (HVA, 5-HIAA, vanillylmandelic acid [VMA] and norepinephrine), and increased levels of 5-hydroxytryptophan, L-dopa and its metabolite (3-O-methyldopa) in body fluids, especially in CSF. Elevated serum concentrations of prolactin (a result of dopamine deficiency) have also been observed. MRI of the brain reveals cerebral atrophy with degenerative changes in the white matter. A screening program, focused on 3-O-methyldopa and VMA, has demonstrated diagnostic promise in high-prevalence populations.

Treatment with neurotransmitter precursors has produced limited clinical improvement. Dopamine and serotonin have no therapeutic value because of their inability to cross the blood–brain barrier. Dopamine agonists (L-dopa/carbidopa, bromocriptine), MAO inhibitors (tranylcypromine), serotonergic agents and high doses of pyridoxine (cofactor for AADC enzyme) have been tried. No treatment of choice has yet emerged. Pyridoxine supplementation in patients harboring the S250F variant may be beneficial. Preimplantation genetic diagnosis after in vitro fertilization has been achieved in the high-prevalence Taiwanese population. The gene encoding AADC (DDC) is on chromosome 7p12.1. The condition is inherited as an autosomal recessive trait; several disease-causing mutations have been reported in different families.

TETRAHYDROBIOPTERIN DEFICIENCY

See Chapter 85.1.

BH4 is the cofactor for PAH (see Fig. 85-1), tyrosine hydroxylase (see Fig. 85-2), tryptophan hydroxylase (see Fig. 85-5), and nitric oxide synthase. It is synthesized from GTP in many tissues (see Fig. 85-1). Deficiencies of enzymes involved in the biosynthesis of BH4 result in inadequate production of this cofactor which causes deficiencies of monoamine neurotransmitters with or without concomitant hyperphenylalaninemia.

Tetrahydrobipterin Deficiency with Hyperphenylalaninemia

See Chapter 85.1.

Tetrahydrobipterin Deficiency Without Hyperphenylalaninemia

Hereditary Progressive Dystonia, Autosomal Dominant Dopa-Responsive Dystonia, Segawa Syndrome, Autosomal Dominant Form

See also Chapter 597.3.

This form of dystonia is caused by GTP cyclohydrolase I deficiency. It is inherited as an autosomal dominant trait and is more common in females than males (4:1).

Clinical manifestations usually start in early childhood with tremor and dystonia of the lower limbs (toe gait), which may spread to all extremities within a few years. Torticollis, dystonia of the arms, and poor coordination may precede dystonia of the lower limbs. Early development is generally normal. Symptoms have an impressive diurnal variation, becoming worse by the end of the day and improving with sleep. Autonomic instability is not uncommon. Parkinsonism may also be present or develop with advancing age. Late presentation in adult life has also been reported, associated with action dystonia (writer’s cramp), torticollis or generalized rigidity with tremor but without postural dystonia. Additionally, limited data on adults suggest symptoms related to serotonin deficiency (sleep disturbance, cognitive impairment and impulsivity).

Laboratory findings show reduced levels of BH4 and neopterin in the CSF without hyperphenylalaninemia. Dopamine and its metabolite (HVA) may also be reduced in CSF. The serotonergic pathway is less affected by this enzyme deficiency; thus, concentrations of serotonin and its metabolites are usually normal. Plasma phenylalanine is normal but an oral phenylalanine loading test (100 mg/kg) produces an abnormally high plasma phenylalanine level with an elevated phenylalanine/tyrosine ratio. The ratio, obtained at the 2nd and 3rd hr postload, in combination with urine neopterin level, has optimal diagnostic specificity and sensitivity. The existence of asymptomatic carriers indicates that other factors or genes may play a role in pathogenesis. The asymptomatic carrier may be identified by the phenylalanine loading test (see above).

Diagnosis may be confirmed by reduced levels of BH4 and neopterin in CSF, through measurement of the enzyme activity, and via molecular genetic analysis (see Chapter 85.1). Clinically, the condition should be differentiated from other causes of dystonias and childhood parkinsonism, especially tyrosine hydroxylation, sepiapterin reductase, and aromatic amino acid decarboxylase deficiencies.

Treatment with L-dopa/carbidopa usually produces dramatic clinical improvement. Oral administration of BH4 is also effective but is rarely used. The gene for GTP cyclohydrolase I (GCH1) is located on chromosome 14q22.2.

Sepiapterin Reductase Deficiency

Sepiapterin reductase is involved in conversion of 6-pyruvoyl-tetrahydropterin to BH4, and also participates in the salvage pathway of BH4 synthesis (see Fig. 85-1). Sepiapterin reductase deficiency results in accumulation of 6-lactoyl-tetrahydropterin, which is converted to sepiapterin nonenzymatically. The majority of sepiapterin is metabolized to BH4 through the salvage pathway in peripheral tissues (see Fig. 85-1), but because of the low activity of dihydrofolate reductase in brain, the amount of BH4 remains insufficient for proper synthesis of dopamine and serotonin. This explains the absence of hyperphenylalaninemia, as well as an explanation for the often delayed diagnosis. Sepiapterin reductase deficiency may also be underdiagnosed as highly specialized CSF assays are required.

Clinical manifestations usually appear within a few months of life. Cardinal manifestations include paroxysmal stiffening, oculogyric crises, and hypotonia. Additional findings include motor and language delays, weakness, limb hypertonia, dystonia, hyperreflexia, and early onset parkinsonism. The symptoms usually have a diurnal variation. Misdiagnosis as cerebral palsy is common.

Diagnosis is established by measurement of CSF neurotransmitters and pterin metabolites which reveal decreased dopamine, HVA, norepinephrine, 5-HIAA and marked elevations of sepiapterin and dihydrobipterin. The serum concentration of prolactin is elevated. The phenylalanine loading test (see above) may have diagnostic utility. Diagnosis may be confirmed by enzyme assay in fibroblasts or via molecular genetic analysis.

Treatment with slowly increasing doses of L-dopa/carbidopa and 5-hydroxytryptophan usually produces dramatic clinical improvement.

The condition is inherited as an autosomal recessive trait; the gene (SPR) for the enzyme is located on chromosome 2p13.2.

DOPAMINE β-HYDROXYLASE DEFICIENCY

See Figure 85-2.

This rare condition has been reported in only a few adult subjects with profound deficits of cardiovascular autonomic regulation resulting in predisposition to orthostatic hypotension. Past histories reveal ptosis, hypotension, hypothermia, hypoglycemia and nasal stuffiness in the neonatal and childhood periods. Presyncopal symptomatology includes dizziness, blurred vision, dyspnea, nuchal discomfort and chest pain; olfactory function remains relatively intact.
Laboratory findings include absence of norepinephrine and epinephrine and their metabolites with elevated levels of dopamine and its metabolite (HVA) in plasma, CSF, and urine. Elevated plasma dopamine may be pathognomonic for this disease. MRI of the brain shows decreased brain volume, consistent with the neurotrophic role of norepinephrine. Treatment with 3,4-dihydroxyphenylserine, which is converted to norepinephrine directly in vivo by the action of AADC, leads to significant improvement in orthostatic hypotension and normalizes noradrenaline and its metabolites. The condition is inherited as an autosomal recessive trait; the gene (DBH) for the enzyme resides on chromosome 9q34.2.

MONOAMINE OXIDASE (MAO) DEFICIENCY
There are 2 MAO isoenzymes: MAO A and MAO B. Both enzymes catalyze oxidative deamination of most biogenic amines in the body, including serotonin (see Fig. 85-5), norepinephrine, epinephrine, and dopamine (see Fig. 85-2). The genes for both isoenzymes are on the X chromosome (A, Xp11.3; B, Xp11.23). Male patients with MAO A deficiency manifest borderline intellectual deficiency and impaired impulse control. MAO B deficiency is found in patients with Norrie disease (see Chapter 622). Patients with isolated MAO B deficiency exhibit normal clinical characteristics and behavior. Combined MAO A and B deficiency causes severe intellectual disability and behavioral problems, associated with more extreme laboratory abnormalities (4–6-fold serotonin elevation in physiologic fluids, elevated O-methylated amine metabolites, and reduced deamination products [VMA, HVA]). A de novo microdeletion in Xp11.3 has been reported twice; the microdeletion in 1 male infant manifested with severe intellectual disability and episodic hypotonia. Dietary intervention (low tyramine, phenylethylamine and dopa/dopamine intake) did not improve the patients’ blood serotonin levels.

γ-AMINOBUTYRIC ACID (GABA)
GABA is the main inhibitory neurotransmitter, which is synthesized in the synapses through decarboxylation of glutamic acid by glutamic acid decarboxylase (GAD). The same pathway is responsible for production of GABA in other organs, especially the kidneys and the β cells of the pancreas. GAD enzyme requires pyridoxine (vitamin B₆) as cofactor. Two GAD enzymes (GAD₆₅ and GAD₆₇) have been identified. GAD₆₅ is the main enzyme in the brain and GAD₆₇ is the major enzyme in the β cells. Antibodies against GAD₆₅ and GAD₆₇ are the major markers for type 1 diabetes and stiff-person syndrome, respectively. Deficiency of neither form of the enzyme has been reported in humans. GABA is catalyzed to succinic acid by 2 enzymes, GABA transaminase and succinic semialdehyde dehydrogenase (SSADH) (see Fig. 85-11).

γ-Aminobutyric Acid Transaminase Deficiency
See Figure 85-11.

Clinical manifestations in the 2 index infant siblings included severe psychomotor retardation, hypotonia, hyperreflexia, lethargy, refractory seizures, and increased linear growth. Increased concentrations of GABA and β-alanine were found in CSF. Evidence of leukodystrophy was noted in the postmortem examination of the brain. A third case showed severe psychomotor retardation, recurrent episodic lethargy and intractable seizures with comparable CSF metabolite abnormalities to those of the index probands. GABA transaminase deficiency is demonstrated in brain and lymphocytes. No effective treatment has been identified. Intervention with vitamin B₆, the cofactor for the enzyme, was without therapeutic benefit. The gene (ABAT), maps to chromosome 16p13.2; the condition is inherited as an autosomal recessive trait.

Succinic Semialdehyde Dehydrogenase Deficiency (γ-Hydroxybutyric Aciduria)
SSADH deficiency is the most common genetic disorder of neurotransmitters (see Fig. 85-11). Clinical manifestations, which usually begin in early infancy, include intellectual disability with disproportionate deficit in expressive language, hypotonia and ataxia; seizures occur in approximately 50% of patients. A diagnosis of autism spectrum disorder occurs disproportionately. Neuropsychiatric morbidity (especially oppositional defiance, obsession-compulsion, and hyperactivity) can be disabling, especially in adolescents and adults. Abnormal EEG findings include background slowing and generalized spike-wave paroxysms, with variable lateralization in hemispheric onset and voltage predominance. Photosensitivities and electrographic status epilepticus of sleep have been reported in combination with difficulties in sleep maintenance and excessive daytime somnolence. MRI of the brain shows an increased T2-weighted hyperintensity involving the globus pallidi, cerebellar dentate nuclei, and subthalamic nuclei, usually showing a bilaterally symmetrical distribution.

The biochemical hallmark, γ-hydroxybutyric acid (GHB), is elevated in physiologic fluids (CSF, plasma, urine) in all patients. Increased concentrations of GABA are also found in CSF. Heightened diagnostic suspicion evolves through documentation of elevated urinary γ-hydroxybutyric acid, and confirmation is achieved by molecular genetic testing.

Treatment remains elusive; vigabatrin (GABA-transaminase inhibitor) has been employed empirically, with mixed outcomes, and there is concern with its use as it further elevates CNS GABA in an already hyper-GABAergic disorder. Additionally, vigabatrin leads to constriction of the visual field and long-term use is contraindicated. Magnesium valproate has shown efficacy for behavioral problems and seizures control in a single case.

The gene for SSADH (ALDH5A1) is located on chromosome 6p22, and inheritance follows an autosomal-recessive pattern. Prenatal diagnosis has been achieved by measurement of GHB in the amniotic fluid, assay of the enzyme activity in the amniocytes or in biopsy specimens of chorionic villi or by DNA analysis.

DEFECTS IN NEUROTRANSMITTERS
TRANSPORTER PROTEINS
More than 20 different proteins are involved in transporting different neurotransmitters across the neuronal membranes. The main function of most of these transporters is to remove the excess neurotransmitters from the synaptic junction (cleft) back into the presynaptic neurons (reuptake). This recycling process not only regulates the precise effect of neurotransmitters at the synaptic junction but also resupplies the presynaptic neurons with neurotransmitters for future use. A few transporter proteins are involved in shuttling neurotransmitters from the neuronal cytoplasm across the membrane of synaptic vesicles for storage (vesicular transporters). Upon neuronal stimulation, these vesicles release a bolus of neurotransmitters via exocytosis. As expected, mutations in transporter proteins interfere with the proper reuptake and storage of neurotransmitters and may result in clinical manifestations similar to those seen in deficiencies of neurotransmitter metabolism themselves. Two conditions caused by mutations of neurotransmitter protein transporters have been described.

Dopamine Transporter Protein Deficiency
This transporter protein is involved in reuptake of dopamine by the presynaptic neurons, and its deficiency causes depletion of dopamine, and hence a dopamine deficiency state. Dopamine transporter protein (DAT) is encoded by SLC6A3 gene on chromosome 5p15.33. Mutation of this gene has been reported in 3 children from 2 unrelated consanguineous families. These children presented with symptoms of infantile parkinsonism-dystonia syndrome. Symptoms of irritability and feeding difficulties started shortly after birth and progressed to hypotonia, lack of head control, parkinsonism, dystonia and global developmental delay by early infancy. Two of the patients were misdiagnosed as having cerebral palsy. MRI of the brain showed no abnormalities.

Examination of the CSF revealed marked elevation of HVA and normal level of 5-HIAAs. The urinary level of HVA, as well as the serum concentration of prolactin, were increased. Diagnosis was established by demonstrating the loss of function mutation in the SLC6A3 gene. No effective treatment has been identified. Treatment with L-dopa/carbidopa did not result in any improvements in clinical or biochemical parameters.
Dopamine–Serotonin Vesicular Transporter Deficiency (Vesicular Monoamine Transporter Deficiency)

This autosomal recessive condition, described in 8 children from a consanguineous Saudi Arabian family is caused by a mutation in the SLC18A2 gene. This gene encodes the vesicular monoamine transporter 2 (VMAT2), which is involved in transporting dopamine and serotonin from the cytoplasm into the synaptic storage vesicles located in the axonal terminals of the presynaptic neurons. Affected children manifested symptoms consistent with deficiencies of dopamine (hypotonia progressing into dystonia, parkinsonism, oculogyric crises), serotonin (sleep and psychiatric disturbances), and norepinephrine-epinephrine (excessive sweating, tremors, temperature instability, postural hypotension and ptosis). Symptoms started at 4 mo of age with hypotonia, lack of head control, inconsolable crying and oculogyric crises. Cognitive development was initially normal but deteriorated with age. No diurnal variation of the symptoms was noted. EEG, MRI, and MRS of the brain, as well as concentrations of all neurotransmitters and their metabolites in the CSF, were within normal limits. Urinary concentrations of 5-HIAA and HVA were moderately increased, whereas those of norepinephrine and epinephrine were decreased.

The phenotype resembles that seen in AADC and BH₄ deficiencies (see above). Proper diagnosis requires mutation analysis of the SLC18A2 gene (located on chromosome 10q25.3). Treatment with L-dopa/carbidopa caused exacerbation of symptoms, whereas treatment with pramipexole, a dopamine receptor agonist, resulted in a favorable clinical response.

HISTIDINE DECARBOXYLASE DEFICIENCY

Decarboxylation of histidine by histidine decarboxylase produces histamine, which functions as a neurotransmitter in the brain. Deficiency of this enzyme (expressed mainly in the posterior hypothalamus) results in deficiency of histamine in the CNS, and in 1 family caused an autosomal dominant form of Tourette syndrome (see Chapter 85.13).

HYPERPROLINEMIA

Psychomotor retardation and seizures are common findings in most patients with hyperprolinemia type I and type II. Patients with type I hyperprolinemia also have an increased risk of developing schizophrenia. The contribution of increased concentration of proline to the pathogenesis of these conditions, however, remains unclear. The neurolologic abnormalities observed in hyperprolinemia type II are mainly because of development of vitamin B₆ dependency in this condition (see Chapter 85.9).

3-PHOSPHOGLYCERATE DEHYDROGENASE DEFICIENCY

See Chapter 85.8.

PHOSPHOSERINE AMINOTRANSFERASE DEFICIENCY

See Chapter 85.8.

NONKETOTIC HYPERGLYCINEMIA

See Chapter 85.7.

Bibliography is available at Expert Consult.

85.12 Urea Cycle and Hyperammonemia (Arginine, Citrulline, Ornithine)

Iraj Rezvani and Marc Yudkoff

Catabolism of amino acids results in the production of free ammonia, which, in high concentration, is toxic to the CNS. Mammals detoxify ammonia to urea through a series of reactions known as the urea cycle (Fig. 85-12), which is composed of 5 enzymes: carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), and arginase. A 6th enzyme, N-acetylglutamate (NAG) synthetase, catalyzes synthesis of NAG, which is an obligatory activator (effector) of the CPS enzyme. Individual deficiencies of these enzymes have been observed and, with an overall estimated prevalence of 1 in 35,000 live births, they are the most common genetic causes of hyperammonemia in infants.

GENETIC CAUSES OF HYPERAMMONEMIA

Hyperammonemia, sometimes severe, occurs in inborn errors of metabolism other than the urea cycle defects (Table 85-3). The pathogenesis for hyperammonemia in some of these conditions is not fully understood, although it is probable that the accumulation of a toxic metabolite—usually an organic acid—compromises function of the urea cycle.

CLINICAL MANIFESTATIONS OF HYPERAMMONEMIA

In the neonatal period, symptoms and signs are mostly related to brain dysfunction and are similar regardless of the cause of the hyperammonemia. The affected infant is normal at birth but becomes symptomatic following the introduction of dietary protein. Refusal to eat, vomiting, tachypnea, and lethargy can quickly progress to a deep coma. Convulsions are common. Physical examination may reveal hepaticomegaly in addition to obtundation. Hyperammonemia can trigger increased intracranial pressure that may be manifested by a bulging fontanelle and dilated pupils.

In infants and older children acute hyperammonemia is manifested by vomiting and neurologic abnormalities such as ataxia, mental confusion, agitation, irritability, and combativeness. These manifestations may alternate with periods of lethargy and somnolence that ultimately progress to coma.

Routine laboratory studies show no specific findings when hyperammonemia is caused by defects of the urea cycle enzymes. Blood urea nitrogen is usually low in these patients; serum pH is usually normal or mildly elevated. There may be mild increases in serum transaminases (alanine aminotransferase, aspartate aminotransferase) because ammonia can cause swelling of hepatic mitochondria. In some patients with severe OTC deficiency, criteria may be met for acute liver failure, as patients with severe OTC-related liver injury may have moderate hyperammonemia (100–400 µmole/L). In infants with organic acids, hyperammonemia is commonly associated with severe acidosis as well as ketonuria. Newborn infants with hyperammonemia are often misdiagnosed as having sepsis; they may succumb without a correct diagnosis. Neuroimaging with CT scanning may reveal cerebral edema. Autopsy is usually unremarkable. It is imperative to measure plasma ammonia levels in any ill infant whose clinical manifestations cannot be explained by an obvious infection.

DIAGNOSIS

The main criterion for diagnosis is hyperammonemia. Each clinical laboratory should establish its own normal values for blood ammonia. Normal newborn values are higher than those of the older child or adult. Levels as high as 100 µmole/L occur in healthy term infants and as high as 150 µmole/L in premature infants. An ill infant usually manifests a blood ammonia level >200 µmole/L. Figure 85-13 illustrates an approach to the differential diagnosis of hyperammonemia in the newborn infant. Careful inspection of individual plasma amino acids commonly reveals abnormalities that may help the diagnosis. In patients with deficiencies of either CPS, OTC, or NAG synthetase, frequent findings include elevations in plasma glutamine and alanine with concurrent decrements in citrulline and arginine. These disorders cannot be differentiated from one another by the plasma amino acid levels alone. A marked increase in urinary orotic acid in patients with OTC deficiency differentiates this defect from CPS deficiency. Differentiation between the CPS deficiency and the NAG synthetase deficiency may require an assay of the respective enzymes or sequencing of the relevant genes. Clinical improvement occurring after oral administration of carbamylglutamate, however, may suggest
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trials in succinic semialdehyde dehydrogenase deficiency, a disorder of GABA
Figure 85-12 Urea cycle: pathways for ammonia disposal and ornithine metabolism. Reactions occurring in the mitochondria are depicted in purple. Reactions shown with interrupted arrows are the alternate pathways for the disposal of ammonia. Enzymes: (1) Carbamyl phosphate synthetase (CPS), (2) ornithine transcarbamylase (OTC), (3) argininosuccinic acid synthetase (AS), (4) argininosuccinate lyase (AL), (5) arginase, (6) ornithine 5-aminotransferase, (7) N-acetylglutamate (NAG) synthetase, (8) citrin. HHH syndrome, hyperammonemia-hyperornithinemia-homocitrullinemia.

Table 85-3 Inborn Errors of Metabolism Causing Hyperammonemia

<table>
<thead>
<tr>
<th>Deficiencies of the urea cycle enzymes</th>
<th>Carbanyl phosphate synthetase</th>
<th>Ornithine transcarbamylase</th>
<th>Argininosuccinate synthetase</th>
<th>Argininosuccinate lyase</th>
<th>Arginase N-acetylglutamate synthetase</th>
<th>Organic acidemias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propionic acidemia</td>
<td>Methylnalonic acidemia</td>
<td>Isovaleric acidemia</td>
<td>β-Ketothiolase deficiency</td>
<td>Multiple carboxylase deficiencies</td>
<td>Medium-chain fatty acid acyl-coenzyme A dehydrogenase deficiency</td>
<td>Glutaric acidemia type I</td>
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<td></td>
<td></td>
<td>3-Hydroxy-3-methylglutaric aciduria</td>
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<td>Lysinuric protein intolerance</td>
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<td></td>
<td></td>
<td>Hyperammonemia-hyperornithinemia-homocitrullinemia syndrome</td>
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<td>Transient hyperammonemia of the newborn</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Congenital hyperinsulinism with hyperammonemia</td>
</tr>
</tbody>
</table>

NAG synthetase deficiency. Patients with a deficiency of ASS, ASL, or arginase have marked increases in the plasma levels of citrulline, argininosuccinic acid, or arginine, respectively. Indeed, the combination of hyperammonemia and marked hypercitrullinemia or argininosuccinic acidemia is virtually pathognomonic for these disorders. Children with urea cycle defects often self-select a low-protein, high-carbohydrate diet, especially those with late-onset disease or symptomatic females with OTC deficiency.

Mass screening of newborn infants identifies patients with ASS, ASL, and arginase deficiencies.

TREATMENT OF ACUTE HYPERAMMONEMIA

Clinical outcome depends mainly on the severity and the duration of hyperammonemia. Serious neurologic sequelae are likely in newborns with severe elevations in blood ammonia (>300 µmole/L) for more than 12 hr. Thus, acute hyperammonemia should be treated promptly and vigorously. The goal of therapy is to lower the concentration of ammonia. This is accomplished in 2 ways: (a) removal of ammonia from the body in a form other than urea and (b) minimizing endogenous protein breakdown and favoring endogenous protein synthesis by providing adequate calories and essential amino acids (Table 85-4). Fluid, electrolytes, glucose (5-15%), and lipids (1-2 g/kg/24 hr) should be infused intravenously together with minimal amounts of protein (0.25 g/kg/24 hr), preferably including essential amino acids. Oral feeding with a low-protein formula (0.5-1.0 g/kg/24 hr) through a nasogastric tube should be started as soon as sufficient improvement in the clinical condition is seen.

Because the kidneys clear ammonia poorly, its removal from the body must be expedited by formation of compounds with a high renal clearance. An important advance in the treatment of hyperammonemia has been the introduction of acylation therapy by using an exogenous organic acid which is acylated endogenously with nonessential amino acids to form a nontoxic compound with high renal clearances. The main organic acids used for this purpose are sodium salts of benzoic acid and phenylacetic acid. Benzoate forms hippurate with endogenous glycine in the liver (see Fig. 85-12). Each mole of benzoate
Defects in Clinical secondary to organic acidemia. Patients with arginase deficiency and in those whose hyperammonemia is citrullinemia and argininosuccinic aciduria. Arginine is not recommended in including the amount of the sodium in the drugs.

**Figure 85-13** Clinical approach to a newborn infant with symptomatic hyperammonemia. CPS, carbamyl phosphate synthetase; HHH syndrome, hyperammonemia-hyperornithinemia-homocitrullinemia; NAG, N-acetylglutamate; OTC, ornithine transcarbamylase.

<table>
<thead>
<tr>
<th>Table 85-4</th>
<th>Treatment of Acute Hyperammonemia in an Infant</th>
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<tbody>
<tr>
<td>1.</td>
<td>Provide adequate calories, fluid, and electrolytes intravenously (10% glucose, NaCl* and intravenous lipids 1 g/kg/24 hr). Add minimal amounts of protein preferably as a mixture of essential amino acids (0.25 g/kg/24 hr) during the 1st 24 hr of therapy.</td>
</tr>
</tbody>
</table>
| 2. | Give priming doses of the following compounds: (To be added to 20 mL/kg of 10% glucose and infused within 1-2 hr)  
  a. Sodium benzoate 250 mg/kg*  
  b. Sodium phenylacetate 250 mg/kg†  
  c. Arginine hydrochloride 200-600 mg/kg as a 10% solution |
| 3. | Continue infusion of sodium benzoate (250-500 mg/kg/24 hr), sodium phenylacetate (250-500 mg/kg/24 hr), and arginine (200-600 mg/kg/24 hr) following the above priming doses. These compounds should be added to the daily intravenous fluid. |
| 4. | Initiate peritoneal dialysis or hemodialysis if above treatment fails to produce an appreciable decrease in plasma ammonia. |

*The concentration of sodium chloride should be calculated to be 0.45-0.9% including the amount of the sodium in the drugs.  
†Sodium from these drugs should be included as part of the daily sodium requirement.  
The higher dose is recommended in the treatment of patients with citrullinemia and argininosuccinic acidemia. Arginine is not recommended in patients with arginase deficiency and in those whose hyperammonemia is secondary to organic acidemia.

removes 1 mole of ammonia as glycine. Phenylacetate conjugates with glutamine to form phenylacetylglutamine, which is readily excreted in the urine. One mole of phenylacetate removes 2 moles of ammonia as glutamine from the body (see Fig. 85-12). A combined formulation of benzoate and phenylacetate (Ammonul) is commercially available for intravenous use.

Another valuable therapeutic adjunct is intravenous infusion of arginine, which is effective in all patients (except those with arginase deficiency). Arginine administration supplies the urea cycle with ornithine and NAG (see Fig. 85-12). In patients with citrullinemia, 1 mole of arginine reacts with 1 mole of ammonia (as carbamyl phosphate) to form citrulline. In patients with argininosuccinic acidemia, 2 moles of ammonia (as carbamyl phosphate and aspartate) react with arginine to form argininosuccinic acid. Citrulline and argininosuccinate are less toxic than ammonia and more readily excreted by the kidneys. In patients with CPS or OTC deficiency, arginine administration is indicated because this amino acid is not produced in sufficient amounts to enable endogenous protein synthesis. Patients with OTC deficiency benefit from supplementation with citrulline (200 mg/kg/24 hr) because 1 mole of citrulline reacts with 1 mole of ammonia (as aspartic acid) to form arginine. Administration of arginine or citrulline is contraindicated in patients with arginase deficiency, a rare condition in which the presenting clinical picture is one of spastic diplegia rather than hyperammonemia (see below). Arginine therapy is of no benefit if hyperammonemia is secondary to an organic acidemia. In a newborn infant with an initial episode of hyperammonemia, arginine should be used until the diagnosis is established.

Benzoate, phenylacetate, and arginine may be administered together for maximal therapeutic effect. A priming dose of these compounds is followed by continuous infusion until recovery from the acute state occurs (see Table 85-4). Both benzoate and phenylacetate are usually supplied as concentrated solutions and should be properly diluted (1-2% solution) for intravenous use. The recommended therapeutic doses of both compounds deliver a substantial amount of sodium to the patient; this amount should be included in calculation of the daily sodium requirement. Benzoate and phenylacetate (or the combined formulation, Ammonul) should be used with caution in newborn infants with hyperbilirubinemia because they may displace bilirubin from albumin; however, there are no documented cases of kernicterus (see Chapter 102.4) reported in neonates with hyperammonemia who have received such therapies. In infants at risk, it is advisable to reduce bilirubin to a safe level before administering benzoate or phenylacetate.

If the foregoing therapies fail within hours to produce any appreciable change in the blood ammonia level, peritoneal dialysis or, preferably, hemodialysis should be used. Exchange transfusion has little effect on reducing total body ammonia; it should be used only if dialysis cannot be employed promptly or when the patient is a newborn infant with hyperbilirubinemia (see above). Hemodialysis dramatically lowers blood ammonia within a few hours, but if it is unavailable or technically
unfeasible, peritoneal dialysis may be used as an alternative. When hyperammonemia is caused by an organic acidemia, peritoneal dialysis effectively removes both the offending organic acid and ammonia.

Oral administration of neomycin limits growth of intestinal bacteria that can produce ammonia. However, this modality is of limited use in patients (such as affected neonates) in whom reduction of hyperammonemia is an urgent priority. Oral lactulose acidifies the intestinal lumen, thereby reducing the diffusion of ammonia across the intestinal epithelium. This agent is of limited applicability in newborns in whom the risks of acidemia and dehydration are high.

There has been interest in the use of cooling as a therapeutic adjunct in newborn infants with metabolic encephalopathies like that caused by hyperammonemia. Clinical studies are in progress to evaluate the efficacy of this approach. There may be considerable lag between the normalization of ammonia and an improvement in the neurologic status of the patient. Several days may be needed before the infant becomes fully alert.

**Long-Term Therapy**

Once the infant is alert, therapy should be tailored to the underlying cause of the hyperammonemia. In general, all patients, regardless of the enzymatic defect, require some degree of protein restriction (1-2 g/kg/24 hr). In patients with defects in the urea cycle, chronic administration of benzoate (250-500 mg/kg/24 hr), phenylacetate (250-500 mg/kg/24 hr), and arginine (200-400 mg/kg/24 hr) or citrulline (in patients with OTC deficiency, 200-400 mg/kg/24 hr) is effective in maintaining blood ammonia levels within the normal range. Arginine and citrulline are contraindicated in patients with argininaemia. Phenylbutyrate may be used in place of phenylacetate, because the patient and the family may not accept the latter owing to its offensive odor. A commercial preparation of the compound is available for oral use (Buphenyl). A significant innovation is the introduction of glycerol phenylbutyrate. This compound, unlike Buphenyl, is not a sodium salt and avoids the consequent coadministration of large amounts of sodium. It is approved for children ≥2 yr but is not yet approved for use in newborns. Benzoate and phenylacetate may lower carnitine levels, but clinical signs of carnitine deficiency or benefit from carnitine supplementation have not yet been demonstrated.

These compounds have been used during pregnancy without obvious teratogenic effect. However, experience is still quite limited and appropriate caution should be exercised.

Growth parameters, especially head circumference, and nutritional indices (blood albumin, prealbumin, pH, electrolytes, amino acids, zinc, selenium) should be followed closely. Long-term care of these patients is best achieved by a team of experienced professionals (pediatrician, nutritionist, child neurologist, metabolic geneticist). Skin lesions resembling acrodermatitis enteropathica (see Chapter 671) have been noted in a few patients with different types of urea cycle defects, presumably from deficiency of essential amino acids, especially arginine, caused by overzealous dietary protein restriction. Catabolic states (infections, fasting) that may trigger hyperammonemia should be avoided. They must be treated vigorously should they occur. It is important that all children with urea cycle defects avoid valproic acid (Depakote) because this drug elevates blood ammonia even in healthy subjects. In patients with CPS, OTC, and ASS deficiencies, acute hyperammonemic attacks may be precipitated by valproate administration.

**CARBAMYL PHOSPHATE SYNTHETASE AND N-ACETYLGlutamate Synthetase Deficiencies**

See Figures 85-12 and 85-13.

Deficiencies of these 2 enzymes produce similar clinical and biochemical manifestations. There is a wide variation in severity of symptoms and in the age at presentation. In near complete enzymatic deficiency, symptoms appear during the first few days or even hours of life with signs and symptoms of hyperammonemia (refusal to eat, vomiting, lethargy, convulsion, and coma). Increased intracranial pressure is present. Late forms (as late as 32 yr of age) may present as an acute bout of hyperammonemia (lethargy, headache, seizures, psychosis) in a seemingly normal individual. Coma and death may occur during these episodes (a previously asymptomatic 26 yr old female died from hyperammonemia during childbirth). Diagnostic confusion with migraine is frequent. Intermediate forms with intellectual disability and chronic subclinical hyperammonemia interspersed with bouts of acute hyperammonemia have also been observed.

**Laboratory findings** include hyperammonemia. The plasma amino-gram commonly shows a marked increase of glutamine and alanine with relatively low levels of citrulline and arginine. These are nondiagnostic changes that occur in hyperammonemia of diverse cause. Urinary orotic acid is usually low or may be absent (see Fig. 85-13).

**Treatment** of acute hyperammonemic attacks and the long-term therapy of the condition is outlined above (see Table 85-4). Patients with NAG synthetase deficiency benefit from oral administration of carbamylglutamate. It is therefore important to differentiate between CPS and NAG synthetase deficiencies by gene sequencing. Deficiency of NAG synthetase is rare in North America.

CPS and NAG synthetase deficiencies are inherited as an autosomal recessive trait; the CPS enzyme is normally present in liver and intestine. The gene (CPS1) is mapped to chromosome 2q34; several disease-causing mutations have been found in different families. The prevalence of the condition is not known. The gene for NAG synthetase (NAGS) is located on chromosome 17q21.31. Neither of these conditions is identified by the mass screening of the newborn infants.

**ORNITHINE TRANSCARBAMYLASE DEFICIENCY**

See Figures 85-12 and 85-13.

In this X-linked partially dominant disorder, the hemizygous males are more severely affected than heterozygous females. The heterozygous females may have a mild form of the disease, but the majority (approximately 75%) is asymptomatic, although investigations indicate subtle neurologic defects even in women without a frank history of hyperammonemia. This is the most common form of all the urea cycle disorders, comprising approximately 40% of cases.

**Clinical manifestations** in a male newborn are usually those of severe hyperammonemia (see above) occurring in the first few days of life. Milder forms of the condition are commonly seen in heterozygous females and in some affected males. MILD forms characteristically have episodic manifestations, which may occur at any age (usually after infancy). Episodes of hyperammonemia (manifested by vomiting and neurologic abnormalities such as ataxia, mental confusion, agitation, combativeness and frank psychosis) are separated by periods of wellness. These episodes usually occur after ingestion of a high-protein diet or as a result of a catabolic state such as infection. Hyperammonemic coma, cerebral edema, and death may occur during one of these attacks. Cognitive development may proceed normally. Mild to moderate intellectual disability, however, is common. Gallstones have been seen in the survivors; the mechanism remains unclear.

The major laboratory finding during the acute attack is hyperammonemia accompanied by marked elevations of plasma concentrations of glutamine and alanine with low levels of citrulline and arginine. The blood level of urea is usually low. A marked increase in the urinary excretion of orotic acid differentiates this condition from CPS deficiency (see Fig. 85-13). Orotate may precipitate in urine as a pink-colored gravel or stones. In the mild form, these laboratory abnormalities may revert to normal between attacks. This form should be differentiated from all the episodic conditions of childhood. In particular, patients with lysinuric protein intolerance (see Chapter 85.14) may demonstrate some features of OTC deficiency, but the former can be differentiated by increased urinary excretion of lysine, ornithine, and arginine and elevated blood concentrations of citrulline.

The diagnosis is most conveniently confirmed by identification of the mutant gene, for which several commercial laboratories offer sequencing. As many as 20% of affected patients demonstrate a normal sequence, perhaps because the mutation involves an intron or a leader peptide. For these cases enzyme assay in a liver biopsy may be indicated. Prenatal diagnosis is feasible by analysis of DNA in amniocytes or chorionic villous samples. An oral protein load, which increases
plasma ammonia and urinary orotic acid levels, may identify asymptomatic heterozygous female carriers. A marked increase in urinary excretion of orotidine after an allopurinol loading test also detects obligate female carriers. Mild cerebral dysfunction may be present in asymptomatic female carriers. The importance of a detailed family history should be emphasized. A history of migraine or protein aversion is common in maternal female relatives of the proband. Indeed, careful scrutiny of the family history may reveal a pattern of unexplained deaths in male newborns in the maternal lineage.

**Treatment of acute hyperammonemic attacks and the long-term therapy of the condition are outlined above.** Citrulline is used in place of arginine in patients with OTC deficiency. Liver transplantation is a successful treatment for patients with OTC deficiency. It even has been performed during infancy.

The gene for OTC has been mapped to the X chromosome (Xp21.1). Many disease-causing mutations (>300) have been identified. The degree of enzyme deficiency and the genotype determine severity of the phenotype in most cases. Mothers of affected infants are expected to be carriers of the mutant gene unless a de novo mutation has occurred. A mother who gave birth to 2 affected male offspring was found to have a normal genotype, suggesting gonadal mosaicism in the mother. This condition is not identified by the mass screening of newborn infants.

**ARGININOSUCCINATE SYNTHETASE (ASS) DEFICIENCY (CITRULLINEMIA)**

See Figures 85-12 and 85-13.

Two clinically and genetically distinct forms of citrullinemia have been identified. The classic form (type I) is caused by the deficiency of the ASS enzyme. The adult form (type II) is caused by the deficiency of a mitochondrial transport protein named citrin.

**Citrullinemia Type I (Classic Citrullinemia)**

This condition is caused by the deficiency of ASS (see Fig. 85-12) and has variable clinical manifestations depending on the degree of the enzyme deficiency. Two major forms of the condition have been identified. The **severe or neonatal form**, which is most common, appears in the first few days of life with signs and symptoms of hyperammonemia (see above). In the **subacute or mild form**, clinical findings such as failure to thrive, frequent vomiting, developmental delay, and dry, brittle hair appear gradually after 1 yr of age. Acute hyperammonemia, triggered by an intercurrent catastrophic state, may bring the diagnosis to light.

**Laboratory findings** are similar to those found in patients with OTC deficiency except that the plasma citrulline concentration is markedly elevated (50-100 times normal) (Fig. 85-13). Urinary excretion of orotic acid is moderately increased; crystalluria as a result of precipitation of orotates may also occur. The **diagnosis** is confirmed by assay of enzyme activity in cultured fibroblasts or by DNA analysis. Prenatal diagnosis is feasible with enzyme assay in cultured amniotic cells or by DNA analysis of cells obtained from chorionic villous biopsy.

**Treatment** of acute hyperammonemic attacks and the long-term therapy of the condition are outlined earlier in this chapter and in Table 85-3. Plasma concentration of citrulline remains elevated at all times, and may increase further after administration of arginine. Although prognosis is poor for symptomatic neonates, patients with the mild disease usually do well on a protein-restricted diet in conjunction with sodium benzoate, phenylbutyrate, and arginine therapy. Mild to moderate cognitive impairment is a common sequela, even in a well-treated patient.

Citrullinemia is inherited as an autosomal recessive trait. The gene (ASS 1) is located on chromosome 9q34.11. Several disease-causing mutations have been identified in different families. The majority of patients are compound heterozygotes for 2 different alleles. The prevalence of the condition is not known. The recent introduction of neonatal screening for urea cycle defects has disclosed affected patients who are ostensibly asymptomatic, even with ingestion of a regular diet. Long-term follow-up is needed to be certain that these individuals do not sustain neurologic sequelae.

**Citrullinemia Resulting From Citrin Deficiency (Citrullinemia Type II)**

Citrin (aspartate-glutamate carrier protein) is a mitochondrial transporter encoded by a gene (SLC25A13) located on chromosome 7q21.3. One of this protein’s functions is to transport aspartate from mitochondria into cytoplasm; aspartate is required for converting citrulline to argininosuccinic acid (see Fig. 85-12). If aspartate is unavailable to the cytoplasmic component of the urea cycle, urea will not be formed at a normal rate and citrulline will accumulate. ASS activity is deficient in the liver of these patients, but no mutation in the gene for ASS has been found. It is postulated that citrin deficiency or its mutated gene interferes with translation of messenger RNA for ASS enzyme in the liver. Mutation in the gene for citrin produces 2 distinct clinical entities. The condition initially was reported almost exclusively in Japan but a few non-Japanese patients have been identified. Two clinical forms of citrin deficiency have been described.

**Neonatal Intrahepatic Cholestasis (Citrullinemia Type II—Neonatal Form)**

Clinical and laboratory manifestations, which usually start before 1 yr of age, include cholestatic jaundice with mild to moderate direct (conjugated) hyperbilirubinemia, marked hyperproteinemia, clotting dysfunction (increased prothrombin time and partial thromboplastin time), and increased serum GGTP and alkaline phosphatase activities; liver transaminases are usually normal. Plasma concentrations of ammonia and citrulline are usually normal, but moderate elevations are reported. There may be increases in plasma concentrations of methionine, tyrosine, alanine, and threonine. Elevated levels of serum galactose have been found even though the enzymes of galactose metabolism are normal. The reason for hypergalactosemia is not known. Marked elevation in the serum level of α-fetoprotein is also present. These findings resemble those of tyrosinemia type I, but unlike the latter condition, urinary excretion of succinylacetone is not elevated (see Chapter 85.2). Liver biopsy shows fatty infiltration, cholestasis with dilated canaliculi, and a moderate degree of fibrosis. The condition is usually self-limiting and the majority of infants recover spontaneously by 1 yr of age with only supportive and symptomatic treatment. Hyperammonemia and hypercitrullinemia, if present, should be treated with a low-protein diet and other appropriate measures (see above). Hepatic failure requiring liver transplantation has occurred in a few cases. Although the condition is commonly seen in Japan, the diagnosis should be considered in any case of unexplained neonatal hepatitis with cholestasis. Data on the long-term prognosis and the natural history of the condition are limited; development into the adult form of the condition (see below) after several years of seemingly asymptomatic hiatus has been observed.

**Citrullinemia Type II, Adult Form (Adult-Onset Citrininemia, Citrullinemia Type II—Mild Form)**

This form starts suddenly in a previously normal individual and manifests with neuropsychiatric symptoms such as disorientation, delirium, delusion, aberrant behavior, tremors, and frank psychosis. Moderate degrees of hyperammonemia and hypercitrullinemia are present. The age at onset is usually between 20 and 40 yr (range: 11-85 yr). Patients who recover from the first episode may have recurrent attacks and most will die within a few years of diagnosis, mainly from cerebral edema. Pancreatitis, hyperlipidemia, and hepatoma are major complications among the survivors. Medical treatment has been mostly ineffective for prevention of future attacks. Indeed, some have speculated that the administration of large amounts of glucose might even prove deleterious, as the citrin transporter is important to the glycolytic pathway. Liver transplantation is the most effective therapy.

Several disease-causing mutations of the gene have been identified in affected Japanese families. The pathogenesis of citrullinemia type II (neonatal and adult forms) remains enigmatic. Although the frequency of homozygosity is relatively high in Japan (1:20,000 people), the clinical condition has a frequency of only 1:100,000 people. This indicates that a substantial number of homozygous individuals remain asymptomatic. Only a few non-Japanese patients have been identified.
ARGININOSUCCINATE LYASE DEFICIENCY (ARGININOSUCCINIC ACIDURIA)

See Figures 85-12 and 85-13.

The severity of the clinical and biochemical manifestations varies considerably. In the neonatal form, signs and symptoms of severe hyperammonemia (see above) develop in the first few days of life and mortality is high. Infants who survive the initial acute episode pursue a subacute or late form that is characterized by intellectual disability, failure to thrive, and hepatomegaly. A common finding is dry and brittle hair (trichorrhexis nodosa). Gallstones have been seen in some survivors. Acute attacks of severe hyperammonemia may occur during a catabolic state.

Laboratory findings include hyperammonemia, moderate elevations in liver enzymes, nonspecific increases in plasma levels of glutamine and alanine, a moderate increase in plasma levels of citrulline (less than that seen in citrullinemia), and marked increase in the concentration of argininosuccinic acid in plasma, urine and spinal fluid (see Fig. 85-13). The levels in the spinal fluid are usually higher than those in plasma. The enzyme is normally present in erythrocytes, the liver and cultured fibroblasts. Prenatal diagnosis is possible by measurement of the enzyme activity in cultured amniotic cells or by identification of the mutant gene. Argininosuccinic acid is also elevated in the amniotic fluid of affected fetuses.

Treatment of acute hyperammonemic attacks and the long-term therapy of the condition are outlined earlier in this chapter. Intellectual disability, persistent hepatomegaly with mild increases in liver enzymes, and bleeding tendencies as a result of abnormal clotting factors are common sequelae. This deficiency is inherited as an autosomal recessive trait. There are 2 genetically distinct arginases in humans. One is cytosolic (ARG1) and is expressed in the liver and erythrocytes, and the other (ARG2) is found in renal and brain mitochondria. The gene for ARG1, the enzyme that is deficient in patients with arginase deficiency, is mapped to chromosome 6q23.2. The role of the mitochondrial enzyme is not well understood; its activity increases in patients with argininemia but has no protective effect. Several disease-causing mutations have been identified in different families.

Clinical manifestations of this rare condition are quite different from those of other urea cycle enzyme defects. The onset is insidious; the infant usually remains asymptomatic in the first few months or years of life. A progressive spastic diplegia with scissoring of the lower extremities, choreothetotic movements, and loss of developmental milestones in a previously normal infant may suggest a degenerative disease of the CNS. Some children were treated for years as cases of cerebral palsy before their arginase deficiency was confirmed. Intellectual disability is a common sequel of the condition. One patient developed type 1 diabetes at age 9 yr while his argininemia was under good control. Liver transplantation has produced promising results but no experience with long term outcome is available. Early detection is feasible through mass screening of newborn infants.

ARGINASE DEFICIENCY (HYPERARGININEMIA)

See Figures 85-12 and 85-13.

This defect is inherited as an autosomal recessive trait. There are 2 arginases, cytosolic (ARG1) and mitochondrial (ARG2), both encoded by the OAT gene on chromosome 7q11.21. Early detection is achieved through mass screening of newborn infants.

Laboratory findings include hyperammonemia, moderate elevations in liver enzymes, nonspecific increases in plasma levels of glutamine and alanine, a moderate increase in plasma levels of citrulline (less than that seen in citrullinemia), and marked increase in the concentration of argininosuccinic acid in plasma, urine and spinal fluid (see Fig. 85-13). The levels in the spinal fluid are usually higher than those in plasma. The enzyme is normally present in erythrocytes, the liver and cultured fibroblasts. Prenatal diagnosis is possible by measurement of the enzyme activity in cultured amniotic cells or by identification of the mutant gene. Argininosuccinic acid is also elevated in the amniotic fluid of affected fetuses.

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HYPERAMMONEMIA-HYPERORNITHINEMIA-HOMOCITRULLINEMIA SYNDROME

In this rare autosomal recessive disorder, the defect is in the transport system of ornithine from the cytosol into the mitochondria, resulting in accumulation of ornithine in the cytosol and a deficiency of this hyperammonemia and lowering plasma arginine levels. Intellectual disability is a common sequel of the condition. One patient developed type 1 diabetes at age 9 yr while his argininemia was under good control. Liver transplantation has produced promising results but no experience with long term outcome is available. Early detection is feasible through mass screening of newborn infants.

TRANSIENT HYPERAMMONEMIA OF THE NEWBORN

The blood concentration of ammonia in full-term infants may be as high as 100 µmole/L, or 2-3 times greater than that of the older child or adult. In premature infants, the upper limit of normal for blood ammonia may be as high as 150 µmole/L. Blood levels approximate the adult normal values after a few weeks of life. These infants are asymptomatic, and follow-up studies up to 18 mo of age have not revealed any significant neurologic deficits.

Severe transient hyperammonemia is observed in some newborn infants. The majority of affected infants are premature and have mild respiratory distress syndrome. Hyperammonemic coma may develop within 2-3 days of life, and the infant may succumb to the disease if treatment is not started immediately. Laboratory studies reveal marked hyperammonemia (plasma ammonia as high as 4,000 µmole/L) with moderate increases in plasma levels of glutamine and alanine. Plasma concentrations of urea cycle intermediate amino acids are usually normal except for citrulline, which may be moderately elevated. The cause of the disorder is unknown. Urea cycle enzyme activities are normal. Treatment of hyperammonemia should be initiated promptly and continued vigorously (see above). Recovery without sequelae is common, and hyperammonemia does not recur even with a normal protein diet.

ORNITHINE

Ornithine, a key intermediate of the urea cycle, is not incorporated into natural proteins. Rather, it is generated in the cytosol from arginine and must be transported into mitochondria, where it is a substrate for the OTC reaction, which forms citrulline. Excess ornithine is catalyzed by 2 enzymes, ornithine 5-aminotransferase, which is a mitochondrial enzyme and converts ornithine to a proline precursor, and ornithine decarboxylase, which resides in the cytosol and converts ornithine to putrescine (see Fig. 85-12). Two genetic disorders feature hyperornithinemia: gyrate atrophy of the retina and hyperammonemia-hyperornithinemia-homocitrullinemia syndrome.

Gyrate Atrophy of the Retina and Choroid

This is a rare, autosomal recessive disorder caused by a deficiency of ornithine 5-aminotransferase (see Fig. 85-12). Approximately 30% of the reported cases are from Finland. Clinical manifestations are limited to the eyes and include night blindness, myopia, loss of peripheral vision, and posterior subcapsular cataracts. These eye changes start between 5 and 10 yr of age and progress to complete blindness by the 4th decade of life. Atrophic lesions in the retina resemble cerebral gyri. These patients usually have normal intelligence and a 10-20-fold increase in plasma levels of ornithine (400-1,400 µmole/L). They have neither hyperammonemia nor increases in plasma concentrations of any other amino acids; plasma levels of glutamate, glutamine, lysine, creatine, and creatinine are moderately decreased. Some patients respond partially to high doses of pyridoxine. An arginine-restricted diet in conjunction with supplemental lysine, proline, and creatine has been successful in reducing plasma ornithine concentration and has produced some clinical improvement. The gene for ornithine 5-aminotransferase (OAT) is mapped to chromosome 10q26.13. Many (at least 60) disease-causing mutations have been identified in different families.

HOMOCITRULLINEMIA SYNDROME

Hypocitrullinemia syndrome is characterized by hyperammonemia, hyperornithinemia, and severe systemic aminoaciduria with severe mental retardation in a familial pattern, which is sometimes associated with a specific craniofacial skeletal defect. The presence of hyperammonemia and hyperornithinemia makes this disease distinct from other forms of homocitrullinemia. Homocitrullinemia syndrome is an autosomal recessive disorder with a prevalence of about 1 in 70,000 live births. The gene for CRTC3, the enzyme that catalyzes the OTC reaction, which forms citrulline. Excess ornithine is catabolized by 2 enzymes, ornithine 5-aminotransferase, which is a mitochondrial enzyme and converts ornithine to a proline precursor, and ornithine decarboxylase, which resides in the cytosol and converts ornithine to putrescine (see Fig. 85-12). Two genetic disorders feature hyperornithinemia: gyrate atrophy of the retina and hyperammonemia-hyperornithinemia-homocitrullinemia syndrome.

HYPERAMMONEMIA-HYPERORNITHINEMIA-HOMOCITRULLINEMIA SYNDROME

In this rare autosomal recessive disorder, the defect is in the transport system of ornithine from the cytosol into the mitochondria, resulting in accumulation of ornithine in the cytosol and a deficiency of this hyperammonemia and lowering plasma arginine levels. Intellectual disability is a common sequel of the condition. One patient developed type 1 diabetes at age 9 yr while his argininemia was under good control. Liver transplantation has produced promising results but no experience with long term outcome is available. Early detection is feasible through mass screening of newborn infants.
85.14 Lysine

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Lysine is catabolized through 2 pathways. In the first pathway, lysine is condensed with α-ketoglutaric acid to form saccharopine. Saccharopine is then catabolized to α-aminoacidic acid semialdehyde and glutamic acid. These first 2 steps are catalyzed by α-aminoacidic acid semialdehyde synthase, which has 2 activities: lysine-ketoglutarate reductase, and saccharopine dehydrogenase (see Fig. 85-14). In the second pathway, lysine is first transaminated and then condensed to its cyclic forms, piperolic acid and piperidine-6-carboxylic acid (P6C). The latter compound (P6C) and its linear form, α-aminoacidic acid semialdehyde, are oxidized to α-aminoacidic acid by the enzyme antiquitin. This is the major pathway for L-lysine in the body and for the L-lysine in the brain (see Fig. 85-14).

Hyperlysinemia, α-aminoacidic acidemia, and α-ketoglutaric acidemia are 3 biochemical conditions that are caused by inborn errors of metabolism of lysine. Individuals with these conditions are usually asymptomatic.

PYRIDOXINE (VITAMIN B₆)-DEPENDENT EPILEPSY

Pyridoxal 5’-phosphate, the active form of pyridoxine, is the cofactor for many enzymes including those involved in the metabolism of neurotransmitters. Intracellular deficiency of pyridoxal 5’-phosphate in the brain may result in a seizure disorder that is refractory to common anticonvulsant agents but is responsive to high doses of pyridoxine. This pyridoxine-dependent epilepsy is seen in the following genetic metabolic conditions:

Antiquitin (α-Aminoacidic Acid Semialdehyde Dehydrogenase) Deficiency

This is the most common cause of pyridoxine-dependent epilepsy. Deficiency of antiquitin results in accumulation of P6C in brain tissue (see Fig. 85-14); P6C reacts with pyridoxal 5’-phosphate and renders it inactive. Large doses of pyridoxine are, therefore, needed to overcome this inactivation.

| Bibliography is available at Expert Consult. |

Figure 85-14 Pathways in the metabolism of lysine. Enzymes: (1) Lysine ketoglutarate reductase, (2) saccharopine dehydrogenase, (3) α-aminoacidic acid semialdehyde/piperidine-6-carboxylic acid (P6C) dehydrogenase (antiquitin), (4) α-aminoacidic acid transferase, (5) α-ketoglutaric acid dehydrogenase, (6) glutaryl-CoA-dehydrogenase. NE, nonenzymatic; PDE, pyridoxine-dependent epilepsy.

Histidine is an essential amino acid only during infancy. Its biosynthetic pathway in older children and adults is poorly understood. Histidine is degraded through the urocanic acid pathway to glutamic acid. Several genetic biochemical aberrations involving the degradative pathway of histidine have been reported, but none has any clinical consequence.

Decarboxylation of histidine by histidine decarboxylase produces histamine. Deficiency of this enzyme is the cause of familial form of Tourette syndrome (see Chapter 85.11).

Bibliography is available at Expert Consult.
Bibliography


Bibliography
Sulfite Oxidase Deficiency (Molybdenum Cofactor Deficiency)
In this rare condition (see Chapter 85.4), accumulation of sulfites causes inhibition of enzymatic activity of antiquitin and accumulation of P6C, which, in turn, causes inactivation of pyridoxal-5'-phosphate and vitamin B₆ dependency.

Hyperprolinemia Type II
In this condition, accumulation of PSC in brain tissue causes inactivation of pyridoxal 5'-phosphate and hence pyridoxine dependency (see Chapter 85.9 and Fig. 85-9).

Hypophosphatasia
Pyridoxal 5'-phosphate is the main circulating form of pyridoxine. Alkaline phosphatase is required for dephosphorylation of pyridoxal 5'-phosphate to generate free pyridoxine which is the only form of vitamin B₆ that can cross the blood–brain barrier and enter the brain cells. Pyridoxine is dephosphorylated intracellularly to form pyridoxal 5'-phosphate. In the infantile form of hypophosphatasia, pyridoxal 5'-phosphate cannot be dephosphorylated to free pyridoxine because of marked deficiency of tissue nonspecific alkaline phosphatase. This results in deficiency of pyridoxine in the brain and pyridoxine-dependent epilepsy (see Chapters 593 and 705).

The main clinical manifestation of pyridoxine-dependent epilepsy caused by antiquitin deficiency is generalized seizures, which usually occur in the first few hours of life and are unresponsive to conventional anticonvulsant therapies. Some mothers of affected fetuses report seizures occurring in the first few hours of life and are unresponsive to conventional anticonvulsant therapies. Some mothers of affected fetuses report

Hyperprolinemia Type II in this condition, accumulation of PSC in brain tissue causes inactivation of pyridoxal 5'-phosphate and hence pyridoxine dependency (see Chapter 85.9 and Fig. 85-9).

Hypophosphatasia Pyridoxal 5'-phosphate is the main circulating form of pyridoxine. Alkaline phosphatase is required for dephosphorylation of pyridoxal 5'-phosphate to generate free pyridoxine which is the only form of vitamin B₆ that can cross the blood–brain barrier and enter the brain cells. Pyridoxine is dephosphorylated intracellularly to form pyridoxal 5'-phosphate. In the infantile form of hypophosphatasia, pyridoxal 5'-phosphate cannot be dephosphorylated to free pyridoxine because of marked deficiency of tissue nonspecific alkaline phosphatase. This results in deficiency of pyridoxine in the brain and pyridoxine-dependent epilepsy (see Chapters 593 and 705).

The main clinical manifestation of pyridoxine-dependent epilepsy caused by antiquitin deficiency is generalized seizures, which usually occur in the first few hours of life and are unresponsive to conventional anticonvulsant therapies. Some mothers of affected fetuses report abnormalities corresponding to the type of seizures; these changes usually normalize after treatment. Neuroimaging may be normal but cerebellar and cerebral atrophy, periventricular hyperintensities, intracerebral hemorrhage, and hydrocephalus may be present. Late-onset forms of the condition (as late as 5 yr of age) have been reported. Consequently, a trial with vitamin B₆ is recommended in any infant with intractable convulsions (see Chapters 593.4 and 593.6).

Laboratory studies reveal increased concentrations of α-aminoacids, glutamic acid is an intermediate in the degradation of lysine (see Fig. 85-14), hydroxylsine, and tryptophan. Glutaric aciduria type I, a disorder caused by a deficiency of glutaryl CoA dehydrogenase, should be differentiated from glutaric aciduria type II, a distinct clinical and biochemical disorder caused by defects in the electron transport system (see Chapter 86.1).

GLUTARIC ACIDURIA TYPE I Glutaric acid is an intermediate in the degradation of lysine (see Fig. 85-14), hydroxylsine, and tryptophan. Glutaric aciduria type I, a disorder caused by a deficiency of glutaryl CoA dehydrogenase, should be differentiated from glutaric aciduria type II, a distinct clinical and biochemical disorder caused by defects in the electron transport system (see Chapter 86.1).

Clinical Manifestations
Affected infants with glutaric aciduria type I may develop normally up to 2 yr of life; macrocephaly is a common finding in these infants and precedes onset of neurologic manifestations. Some affected infants may also show subtle neurologic symptoms, such as hypotonia, irritability, and feeding problems, during this seemingly asymptomatic period. The onset of the condition is usually heralded by acute encephalopathic findings such as loss of normal developmental milestones (head control, sitting), choreothetosis, seizures, generalized rigidity, opisthotonos, and dystonia. These symptoms may occur suddenly in a seemingly normal infant after a minor infection. Recovery from the first attack usually occurs slowly, but some residual neurologic abnormalities, especially dystonia and dystonic movements may persist. Additional acute attacks resembling the first one usually occur during episodes of intercurrent infections or catabolic states. In some patients, these signs and symptoms may develop gradually in the first few years of life; hypotonia and choreothetosis may gradually progress into rigidity and dystonia (“insidious form”). Acute episodes of metabolic decompensation with vomiting, ketosis, seizures, and coma also occur in this form after infection or other catabolic states. Death usually occurs in the 1st decade of life during one of these episodes. The affected infants are prone to development of subdural hematoma and retinal hemorrhage following minor falls and head trauma. This may be misdiagnosed as child abuse. The intellectual abilities usually remain relatively normal in most patients.

Laboratory Findings
During acute episodes, mild to moderate metabolic acidosis and ketosis may occur. Hypoglycemia, hyperammonemia, and elevations of serum transaminases are seen in some patients. High concentrations of glutaric acid are usually found in urine, blood, and CSF. 3-Hydroxylutaric acid may also be present in the urine. Plasma concentrations of amino acids are usually within normal limits. Laboratory findings may be unremarkable between attacks. Severely affected children without glutaric aciduria have also been reported (“low excretors”). In some of these patients, the glutaric acid is elevated only in the spinal fluid. In any child with progressive dystonia and dyskinesia, activity of the enzyme glutaryl CoA dehydrogenase should be measured in leukocytes or cultured fibroblasts as urinary glutaric acid may not be elevated in those patients who are the “low excretors.” Neuroimaging of the brain may reveal macrocephaly, increased extraaxial (particularly frontal) fluid, striatal lesions, dilated lateral ventricles, cortical atrophy (mainly in frontotemporal region), and fibrosis.

Treatment
A low-protein diet (especially a diet restricted in lysine and tryptophan) and high doses (200–300 mg/24 hr) of riboflavin (the coenzyme for glutaryl CoA dehydrogenase) and L-carnitine (50–100 mg/kg/24 hr orally) produce a dramatic decrease in the levels of glutaric acid in body fluids, but their effects on the clinical outcome have been variable. Early diagnosis (through newborn screening) with prevention and aggressive treatment of intercurrent catabolic states (infections) are shown to minimize striatal insults and assure a more favorable prognosis. The addition of a GABA analog (baclofen) and valproic acid to the therapeutic regimen produces improvement in some affected children.

The condition is inherited as an autosomal recessive trait. The prevalence is estimated at 1:100,000 live births worldwide. The condition is more prevalent in some ethnic populations (Canadian Oji-Cree Indians, Irish travelers, black South Africans, Swedes, and the Old Order Amish population in the United States). The gene for glutaryl CoA dehydrogenase (GCDH) is located on chromosome 19p13.2 and many disease-causing mutations have been reported in different families. A single mutation (A421V) accounts for all the patients from the Lancaster County (Pennsylvania) Old Order Amish community.

Prenatal diagnosis may be accomplished by demonstrating increased concentrations of glutaric acid in amniotic fluid, by the assay of the enzyme activity in amniocytes or chorionic villous samples, or by identification of the mutant gene.

LYSINURIC PROTEIN INTOLERANCE (FAMILIAL PROTEIN INTOLERANCE)
This rare autosomal recessive disorder is caused by a defect in the transport of the cationic amino acids lysine, ornithine, and arginine in both intestine and kidneys. Unlike patients with cystinuria, urinary excretion of cystine is not increased in these patients. Deficiency of the transporter protein in this condition causes multisystem manifestations, which start initially with gastrointestinal symptoms. Refusal to feed, nausea, aversion to protein, vomiting, and mild diarrhea, which may result in failure to thrive, wasting, and hypotonia, start shortly

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after birth. Breastfed infants usually remain asymptomatic until shortly after weaning. This may be because of the low protein content of breast milk. Episodes of hyperammonemia may occur after ingestion of a high-protein diet. Mild to moderate hepatosplenomegaly, osteoporosis, sparse brittle hair, thin extremities with moderate centripetal adiposity, and growth retardation are common physical findings in patients whose condition has remained undiagnosed. Mental development is usually normal, but moderate intellectual disability has been observed in 20% of patients.

Progressive interstitial pneumonia with bouts of acute exacerbation commonly occurs in these patients. This usually progresses to severe alveolar proteinosis. Clinical manifestations include progressive exertional dyspnea, fatigue, cough, diminished breath sound, and inspiratory rales; cyanosis may develop in older patients. Some patients have remained undiagnosed until the appearance of pulmonary manifestations. Radiographic evidence of pulmonary fibrosis has been observed in up to 65% of patients without clinical manifestations of pulmonary involvement.

Renal involvement is manifested initially by proteinuria, hematuria, and elevation of serum creatinine, which may progress to end-stage renal failure. Renal tubular involvement with findings compatible with Fanconi syndrome may also be present. Renal biopsy reveals pathologic findings consistent with glomerulonephritis and tubulointerstitial nephritis. Hematologic findings of anemia, leukopenia, and thrombocytopenia may also be present. A condition resembling hemophagocytic lymphohistiocytosis/macrophage activation syndrome has also been reported. Immunologic abnormalities (impaired lymphocyte function, abnormalities in immune globulins, hypocomplementemia), hypercholesterolemia, hypertriglyceridemia, and acute pancreatitis have also been reported in these patients.

Laboratory findings may reveal hyperammonemia and an elevated concentration of urinary orotic acid, which develop after protein feeding. Plasma concentrations of lysine, arginine, and ornithine are usually mildly decreased, but urinary levels of these amino acids, especially lysine, are greatly increased. The pathogenesis of hyperammonemia is not well understood. All enzymes of the urea cycle are normal. Hyperammonemia may be related to disruption of the urea cycle secondary to deficiency of arginase and ornithine. However, in patients with cystinuria who also have defects in the transport of lysine, arginine, and ornithine in both intestine and kidneys, hyperammonemia is not observed. Plasma concentrations of alanine, glutamine, serine, glycine, proline, and citrulline are usually increased. Anemia, increased serum levels of ferritin, LDH, and thyroxine-binding globulin, have also been observed in these patients. This condition should be differentiated from hyperammonemia caused by urea cycle defects (see Chapter 85.12), especially in heterozygous females with OTC deficiency. Increased urinary excretion of lysine, ornithine, and arginine and elevated blood levels of citrulline are not seen in patients with OTC deficiency.

The transport defect in this condition resides in the basolateral (anti-luminal) membrane of enterocytes and renal tubular epithelia. This explains the observation that cationic amino acids are unable to cross these cells even when administered as dipeptides. Lysine in the form of dipeptide crosses the luminal membrane of the enterocytes but hydrolyzes to free lysine molecules in the cytoplasm. Free lysine, unable to cross the basolateral membrane of the cells, diffuses back into the lumen.

Treatment with a low-protein diet (1.0-1.5 g/kg/24 hr) supplemented with citrulline (100 mg/kg/day) has produced biochemical and clinical improvements. Episodes of hyperammonemia should be treated promptly (see Chapter 85.12). Supplementation with lysine is not useful because it is poorly absorbed and tends to produce diarrhea and abdominal pain. Diet therapy has no effect in prevention or amelioration of the multisystem manifestations. Treatment with high doses of prednisone has been effective in the management of acute pulmonary complications in some patients. Bronchopulmonary lavage is the treatment of choice for patients with alveolar proteinosis. The condition is most prevalent in Finland and Japan where the prevalence is 1:60,000 and 1:57,000 live births, respectively.

The gene for lysinuric protein intolerance (SLC7A7) is mapped to chromosome 14q11.2, and several disease-causing mutations have been identified in different families. Pregnancies in affected mothers have been complicated by anemia, thrombocytopenia, toxemia, and bleeding, but offspring have been normal.

Bibliography is available at Expert Consult.

85.15 Aspartic Acid (Canavan Disease)
Kimberlee M. Matalon and Reuben K. Matalon

N-Acetylaspartic acid, a derivative of aspartic acid, is synthesized in the brain and is found in a high concentration similar to glutamic acid. The exact function of N-acetylaspartic acid is unknown, but it may serve as a reservoir for acetate, which is needed for myelin synthesis. Aspartoacylase, cleaves the N-acetyl group from N-acetylaspartic acid. Deficiency of aspartoacylase leads to Canavan disease, a severe leukodystrophy, characterized by excessive excretion of N-acetylaspartic acid and spongy degeneration of the white matter of the brain. Canavan disease is an autosomal recessive disorder and is more prevalent in individuals of Ashkenazi Jewish descent than in other ethnic groups. Aspartoacylase deficiency can be determined in skin fibroblasts, but the diagnosis is easy to ascertain by increased excretion of N-acetylaspartic acid in the urine. The gene for Canavan disease has been cloned, and mutations can be measured in patients, family members, and at-risk populations.

ETIOLOGY AND PATHOLOGY
The deficiency of the enzyme aspartoacylase leads to the accumulation of N-acetylaspartic acid in the brain, especially in white matter, and massive urinary excretion of this compound. Excessive amounts of N-acetylaspartic acid are also present in the blood and CSF. Brain biopsies of patients with Canavan disease show spongy degeneration of the myelin fibers, astrocytic swelling, and elongated mitochondria. There is striking vacuolization and astrocytic swelling in white matter. Electron microscopy reveals distorted mitochondria. As the disease progresses, the ventricles enlarge, owing to cerebral atrophy.

CLINICAL MANIFESTATIONS
The severity of Canavan disease covers a wide spectrum. Infants usually appear normal at birth and may not manifest symptoms of the disease until 3–6 mo of age, when they develop progressive macrocephaly, severe hypertonia, persistent head lag, and delayed milestones. As the disease progresses, there is spasticity, joint stiffness, and contractures. Optic atrophy and seizures develop. Feeding difficulties, poor weight gain, and gastroesophageal reflux may occur in the 1st yr of life; swallowing deteriorates, and nasogastric feeding or permanent gastrostomy may be required. Most patients die in the 1st decade of life; with improved nursing care, they may survive through the second decade.

ATYPICAL CANAVAN DISEASE
Juvenile or mildly affected patients with Canavan disease usually present with mild developmental delay, although 1 patient also had a large head and retinitis pigmentosa. These children have moderately increased urinary excretion of N-acetylaspartic acid, which suggests Canavan disease. Brain MRI demonstrates increased signal intensity in the basal ganglia rather than global white matter disease, sometimes leading to confusion with mitochondrial disease.

Diagnosis
In a typical patient with Canavan disease, CT scan and MRI reveal diffuse white matter degeneration, primarily in the cerebral hemispheres, with less involvement of the cerebellum and brainstem (Fig. 85-15). Repeated evaluations may be required. MRS performed at the time MRI is done can show the high peak of N-acetylaspartic acid, suggesting Canavan disease. The definitive diagnosis can be established by finding elevated amounts of N-acetylaspartic acid in the urine or
Bibliography
Patients with juvenile or mild forms of Canavan disease have been compound heterozygotes with a mild mutation on one allele and a severe mutation on the other mutation. Mild mutations include p.Tyr288Cys and p.Arg71His.

**Treatment and Prevention**

No specific treatment is available. Feeding problems and seizures should be treated on an individual basis. Genetic counseling, carrier testing, and prenatal diagnosis are the only methods of prevention. Gene therapy attempts in children with Canavan disease have shown lack of long-term adverse events, some decrease in the brain elevation of \(N\)-acetylaspartic acid, improved seizure frequency, and stabilization of overall clinical status. There are ongoing trials of glycerol-triacetate as a supplement for acetate deficiency.

*Bibliography is available at Expert Consult.*

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**Figure 85-15** Axial T-weighted MRI of a 2 yr old patient with Canavan disease. Extensive thickening of the white matter is seen.
Bibliography


Mitochondrial β-oxidation of fatty acids is an essential energy-producing pathway. It is a particularly important pathway during prolonged periods of starvation, and during periods of reduced caloric intake because of gastrointestinal illness or increased energy expenditure during febrile illness. Under these conditions, the body switches from using predominantly carbohydrate to predominantly fat as its major fuel. Fatty acids are also important fuels for exercising skeletal muscle and are the preferred substrate for the heart. In these tissues, fatty acids are completely oxidized to carbon dioxide and water. The end products of hepatic fatty acid oxidation are the ketone bodies β-hydroxybutyrate and acetoacetate. These cannot be oxidized by the liver but are exported to and serve as important fuels in peripheral tissues, particularly the brain, which can partially substitute ketone bodies for glucose during periods of fasting.

Genetic defects have been identified in nearly all of the known steps in the fatty acid oxidation pathway; all are recessively inherited (Table 86-1). Clinical manifestations characteristically involve those tissues with a high β-oxidation flux, including liver, skeletal, and cardiac muscle. The most common presentation is an acute episode of life-threatening coma and hypoglycemia induced by a period of fasting because of defective hepatic ketogenesis. Other manifestations may include chronic cardiomyopathy and muscle weakness or exercise-induced acute rhabdomyolysis. The fatty acid oxidation defects can often be asymptomatic during periods when there is no fasting stress. Acutely presenting disease may be misdiagnosed as Reye syndrome or, if fatal, as sudden unexpected infant death. Fatty acid oxidation disorders are easily overlooked because the only specific clue to the diagnosis may be the finding of inappropriately low concentrations of urinary ketones in an infant who has hypoglycemia. Genetic defects in ketone body utilization may also be overlooked because ketosis is an expected finding with fasting hypoglycemia. In some circumstances, clinical manifestations appear to arise from toxic effects of fatty acid metabolites rather than inadequate energy production. These include disorders (long chain 3-hydroxyacyl dehydrogenase
### Table 86-1  Mitochondrial Fatty Acid Oxidation Disorders—Clinical and Biochemical Features

<table>
<thead>
<tr>
<th>ENZYME DEFICIENCY</th>
<th>GENE</th>
<th>CLINICAL PHENOTYPE</th>
<th>LABORATORY FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carnitine transporter</td>
<td>OCTN2 SLC22A5</td>
<td>Cardiomyopathy, skeletal myopathy, liver disease, sudden death, endocardial fibroelastosis, prenatal and newborn screening diagnosis reported</td>
<td>↓ Total and free carnitine, normal acylcarnitines, acylglycine, and organic acids</td>
</tr>
<tr>
<td>Long-chain fatty acid transporter</td>
<td>FATP1-6</td>
<td>Rare, acute liver failure in childhood requiring liver transplantation</td>
<td>Reduced intracellular C14-C16 fatty acids, reduced fatty acid oxidation</td>
</tr>
<tr>
<td>Carnitine palmitoyl transferase-I</td>
<td>CPT-IA</td>
<td>Liver failure, renal tubulopathy, and sudden death. Prenatal and newborn screening diagnosis reported, maternal preeclampsia, HELLP syndrome association described in a few patients</td>
<td>Normal or ↑ free carnitine, normal acylcarnitines, acylglycine, and organic acids</td>
</tr>
<tr>
<td>Carnitine acylcarnitine translocase</td>
<td>CACT SLC25A20</td>
<td>Chronic progressive liver failure, persistent ↑ NH₃, hypertrophic cardiomyopathy. Newborn screening diagnosis reported</td>
<td>Normal or ↓ free carnitine, abnormal acylcarnitine profile</td>
</tr>
<tr>
<td>Carnitine palmitoyl transferase-II</td>
<td>CPT-II</td>
<td>Early and late onset types. Liver failure, encephalopathy, skeletal myopathy, cardiomyopathy, renal cystic changes, newborn screening diagnosis reported. Adult form with acute rhabdomyolysis, myoglobinuria</td>
<td>Normal or ↓ free carnitine, abnormal acylcarnitine profile</td>
</tr>
<tr>
<td>Short-chain acyl-CoA dehydrogenase</td>
<td>SCAD ACADS</td>
<td>Clinical phenotype is unclear. Many individuals appear to be normal. Others have a variety of inconsistent signs and symptoms. Subset may have severe manifestations of unclear relationship to biochemical defects. Newborn screening diagnosis reported; significance being questioned</td>
<td>Normal or ↓ free carnitine, elevated urine ethylmalonic acid, inconsistently abnormal acylcarnitine profile</td>
</tr>
<tr>
<td>Medium-chain acyl-CoA dehydrogenase</td>
<td>MCAD ACADM</td>
<td>Hypoglycemia, hepatic encephalopathy, sudden death. Newborn screening diagnosis possible, maternal preeclampsia, HELLP syndrome association described rarely</td>
<td>Normal or ↓ free carnitine, ↑ plasma acylglycine, plasma C14-C16 free fatty acids, ↑ C10-C14 acyl-carnitine</td>
</tr>
<tr>
<td>Very long-chain acyl-CoA dehydrogenase</td>
<td>VLCAD ACADVL</td>
<td>Dilated cardiomyopathy, arrhythmias, hypoglycemia, and hepatic steatosis. Late-onset, stress-induced rhabdomyolysis, episodic myopathy. Prenatal and newborn screening diagnosis possible.</td>
<td>Normal or ↓ free carnitine, ↑ plasma C14-C16 free fatty acids, ↑ C16-OH and C18-OH carnitines of acyl:free carnitine, inconsistently abnormal urine organic acid and acylglycines</td>
</tr>
<tr>
<td>ETF dehydrogenase*</td>
<td>ETF-DH</td>
<td>Nonketotic fasting hypoglycemia, congenital anomalies, milder forms of liver disease, cardiomyopathy, and hepatic steatosis. Newborn screening diagnosis reported</td>
<td>Normal or ↓ free carnitine, increased ratio of acyl-free carnitine, ↑ acylcarnitine, urine organic acid and acylglycines</td>
</tr>
<tr>
<td>ETF-α*</td>
<td>α-ETF</td>
<td>Nonketotic fasting hypoglycemia, congenital anomalies, liver disease, cardiomyopathy, and skeletal myopathy also described. Newborn screening diagnosis reported</td>
<td>Normal or ↓ free carnitine, increased ratio of acyl-free carnitine, ↑ acylcarnitine, urine organic acid and acylglycines</td>
</tr>
<tr>
<td>ETF-β*</td>
<td>β-ETF</td>
<td>Fasting hypoglycemia, congenital anomalies, liver disease, cardiomyopathy, and skeletal myopathy also described. Newborn screening diagnosis reported</td>
<td>Normal or ↓ free carnitine, increased ratio of acyl-free carnitine, ↑ acylcarnitine, urine organic acid and acylglycines</td>
</tr>
<tr>
<td>Short-chain L-3-hydroxyacyl-CoA dehydrogenase</td>
<td>SCHAD HADH</td>
<td>Hyperinsulinemic hypoglycemia, cardiomyopathy, myopathy. Newborn screening diagnosis reported</td>
<td>Normal or ↓ free carnitine, elevated free fatty acids, inconsistently abnormal urine organic acid, ↑3-OH glutarate. ↑ plasma C₇-OH acylcarnitine</td>
</tr>
<tr>
<td>Long-chain L-3-hydroxyacyl-CoA dehydrogenase</td>
<td>LHAD HADH-A</td>
<td>Newborn screening diagnosis reported, maternal preeclampsia, HELLP syndrome, and AFLP association described frequently. See also MTP below for clinical manifestations</td>
<td>Normal or ↓ free carnitine, increased ratio of acyl-free carnitine, ↑ free fatty acids, ↑ C12-OH and C14-OH carnitines</td>
</tr>
<tr>
<td>MTP</td>
<td>HADH-A, HADH-B</td>
<td>Severe cardiac and skeletal myopathy, hypoglycemia, acidosis, hyper NH₃, sudden death, elevated liver enzymes, retinopathy. Maternal preeclampsia, HELLP syndrome, and AFLP association described frequently</td>
<td>Normal or ↓ free carnitine, increased ratio of acyl-free carnitine, ↑ free fatty acids, ↑ C14-OH and C16-OH carnitines</td>
</tr>
<tr>
<td>Long-chain 3-ketoacyl-CoA thiolase</td>
<td>LKAT HADH-B</td>
<td>Severe neonatal presentation, hypoglycemia, acidosis, ↑ creatine kinase, cardiomyopathy, neuropathy, and early death</td>
<td>Normal or ↓ free carnitine, increased ratio of acyl-free carnitine, ↑ free fatty acids, ↑ 2-trans, 4-cis-decadienoylcarnitine</td>
</tr>
<tr>
<td>2,4-Dienoyl-CoA reductase</td>
<td>DECR1</td>
<td>Only 1 patient described, hypotonia in the newborn, mainly severe skeletal myopathy and respiratory failure. Hypoglycemia rare</td>
<td>Normal or ↓ free carnitine, ↑ acyl-free carnitine ratio, normal urine organic acids and acylglycines</td>
</tr>
</tbody>
</table>

Continued
Metabolic Disorders

Part XI

Mitochondrial Fatty Acid Oxidation Disorders—Clinical and Biochemical Features—cont’d

Table 86-1 Mitochondrial Fatty Acid Oxidation Disorders—Clinical and Biochemical Features—cont’d

<table>
<thead>
<tr>
<th>ENZYME DEFICIENCY</th>
<th>GENE</th>
<th>CLINICAL PHENOTYPE</th>
<th>LABORATORY FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMG CoA synthetase</td>
<td>HMGCS2</td>
<td>Hypoketosis and hypoglycemia, rarely myopathy</td>
<td>Elevated total plasma fatty acids, enzyme studies in biopsied liver may be diagnostic, genetic testing is preferred</td>
</tr>
<tr>
<td>HMG CoA lyase</td>
<td>HMGCL</td>
<td>Hypoketosis and hypoglycemia, rarely myopathy</td>
<td>Normal free carnitine, ↑ C2-OH, and methylglutaryl-carnitine, enzymes studies in fibroblasts may be diagnostic</td>
</tr>
</tbody>
</table>

*Also known as glutaric acidemia type II or multiple acyl-CoA dehydrogenase deficiency (MADD). APLP, acute fatty liver of pregnancy; CoA, coenzyme A; ETF, electron transport flavoprotein; HELLP, hemolysis, elevated liver enzymes, low platelets; MTP, mitochondrial trifunctional protein; NH3, ammonia. From Shekhawat PS, Matern D, Strauss AW: Fetal fatty oxidation disorders, their effect on maternal health and neonatal outcome: impact of expanded newborn screening on their diagnosis and management, Pediatr Res 57:788–84R, 2005.

[...]

HMG-CoA synthetase, HMG-CoA lyase, and CPT-IA deficiencies that do not manifest secondary carnitine deficiency. Significant exceptions to this rule are the plasma membrane carnitine transporter, CPT-IA carnitine for transport at the plasma membrane. Significant exceptions to this rule are the plasma membrane carnitine transporter, CPT-IA carnitine for transport at the plasma membrane. Significant exceptions to this rule are the plasma membrane carnitine transporter, CPT-IA carnitine for transport at the plasma membrane.

The liver may be slightly enlarged with fat deposition. Attacks are rare until the infant is beyond the first few months of life, presumably because of more frequent feedings at a younger age. Affected older infants are at higher risk of illness as they begin to fast through the night or are exposed to fasting stress during an intercurrent childhood illness. Presentation in the first days of life with neonatal hypoglycemia has been reported in newborns that were fasted inadvertently. Diagnosis of MCAD has occasionally been documented in previously healthy teenage and adult individuals, indicating that even patients who have been asymptomatic in infancy are still at risk for metabolic decompensation if exposed to sufficient periods of fasting. An unknown number may remain asymptomatic. Prior to routine newborn screening testing, as many as 25% of MCAD deficient cases died or suffered severe brain damage from their first episode. Most patients are now diagnosed in the newborn period by blood spot acylcarnitine screening, allowing the initiation of early treatment and prevention of many of the severe signs and symptoms.

**Laboratory Findings**

During acute episodes, hypoglycemia is usually present. Plasma and urinary ketone concentrations are inappropriately low (hypoketotic hypoglycemia). Because of the hypoketonemia, there is little or no metabolic acidosis, which is expected to be present in many children with hypoglycemia. Tests of liver function are abnormal, with elevations of liver enzymes (alanine aminotransferase, aspartate aminotransferase), elevated blood ammonia, and prolonged prothrombin and partial thromboplastin times. Liver biopsy at times of acute illness shows microvesicular or macrovesicular steatosis from triglyceride accumulation. During fasting stress or at times of acute illness, urinary organic acid profiles by gas chromatography/mass spectrometry show inappropriately low concentrations of ketones and elevated levels of medium-chain dicarboxylic acids (adipic, suberic, and sebacic acids) that derive from microsomal and peroxisomal omega oxidation of accumulated medium-chain fatty acids. Plasma and tissue concentrations of total carnitine are reduced to 25-50% of normal, and the fraction of total esterified carnitine is increased. This pattern of secondary carnitine deficiency is seen in most fatty acid oxidation defects and reflects competition between increased acylcarnitine levels and free carnitine for transport at the plasma membrane. Significant exceptions to this rule are the plasma membrane carnitine transporter, CPT-1A and β-hydroxy-β-methylglutaryl-CoA (HMG-CoA) synthase deficiencies that do not manifest secondary carnitine deficiency.

Diagnostic metabolite patterns include increased plasma C9:0, C10:0, and C10:1 acylcarnitine species and increased urinary acylglycines including hexanoyl-propionyl, suberyl-propionyl, and 3-phenylpropionyl glycines. Newborn screening programs using tandem mass spectrometry, which almost all babies born in the United States receive, can diagnose presymptomatic MCAD deficiency based on the detection of the abnormal acylcarnitines in filter paper blood spots. In many cases, the diagnosis can be confirmed by finding the common A985G mutation. A second common variant, T199C, has been detected in infants with...
Figure 86-1 Mitochondrial fatty acid oxidation. Carnitine enters the cell through the action of the organic cation/carnitine transporter (OCTN2). Palmitate, a typical 16-carbon long-chain fatty acid, is transported across the plasma membrane and can be activated to form a long-chain (LC) fatty acyl coenzyme A (CoA). It then enters into the carnitine cycle, where it is transesterified by carnitine palmitoyltransferase-I (CPT-I), translocated across the inner mitochondrial membrane by carnitine/acylcarnitine translocase (TRANS), and then reconverted into a long-chain fatty acyl-CoA by carnitine palmitoyltransferase-II (CPT-II) to undergo β-oxidation. Very-long-chain acyl-CoA dehydrogenase (VLCAD/LCAD) leads to the production of (C_{16}-C_{18}) 2,3 enoyl CoA. Mitochondrial trifunctional protein (MTP) contains the activities of enoyl CoA hydratase (hydratase), 3-OH-hydroxyacyl-CoA dehydrogenase (3-OH-ACD), and β-ketothiolase (thiolase). Acetyl-CoA, reduced form of flavin adenine dinucleotide (FADH), and reduced form of nicotinamide adenine dinucleotide (NADH) are produced. Medium- and short-chain fatty acids (C8-4) can enter the mitochondrial matrix independent of the carnitine cycle. Medium-chain acyl-CoA dehydrogenase (MCAD), short-chain acyl-CoA dehydrogenase (SCAD), and short-chain hydroxy acyl-CoA dehydrogenase (SCHAD) are required. Acetyl-CoA can then enter the Krebs (TCA) cycle. Electrons are transported from FADH to the respiratory chain via the electron transfer flavoprotein (ETF) and the electron transfer flavoprotein dehydrogenase (ETF-DH). NADH enters the electron transport chain through complex I. In liver, acetyl-CoA can be converted into hydroxymethylglutaryl (HMG) CoA by β-hydroxy-β-methylglutaryl-CoA synthase (HMG CoA synthase) and then the ketone body acetoacetate by the action of β-hydroxy-β-methylglutaryl-CoA lyase (HMG-CoA lyase).

characteristic acylcarnitines in newborn screening tests. Interestingly, this allele has not been seen to date in symptomatic MCAD patients; it may represent a milder mutation.

Treatment
Acute illnesses should be promptly treated with intravenous fluids containing 10% dextrose to treat or prevent hypoglycemia and to suppress lipolysis as rapidly as possible (see Chapter 92). Chronic therapy consists of avoiding fasting. This usually requires simply adjusting the diet to ensure that overnight fasting periods are limited to <10-12 hr. Restricting dietary fat or treatment with carnitine is controversial. The necessity for active therapeutic intervention for individuals with the T199C variant has not yet been established.

Prognosis
Up to 25% of unrecognized patients may die during their first attack of illness. There is a frequent history of a previous sibling death that is presumed to be from an unrecognized MCAD deficiency. Some patients may suffer permanent brain injury during an attack of profound hypoglycemia. The prognosis for survivors without brain damage is excellent because progressive cognitive impairment or cardiomyopathy does not occur in MCAD deficiency. Muscle pain and reduced exercise tolerance may become evident with increasing age. Fasting tolerance improves with age and the risk of illness decreases. Because as many as 35% of affected patients have never had an episode, testing of siblings of affected patients is important to detect asymptomatic family members.

Very-Long-Chain Acyl-Coenzyme A Dehydrogenase Deficiency
Very-long-chain acyl-CoA dehydrogenase (VLCAD) deficiency is the second most commonly diagnosed disorder of fatty acid oxidation. It was originally termed long-chain acyl-CoA dehydrogenase deficiency before the existence of the inner mitochondrial membrane-bound VLCAD was known. All patients previously diagnosed as having long-chain acyl-CoA dehydrogenase deficiency have VLCAD gene defects. Patients with VLCAD deficiency have no ability to oxidize physiologic long-chain fatty acids and are usually more severely affected than those with MCAD deficiency who have a milder oxidative defect. VLCAD deficiency presents earlier in infancy and has more chronic problems...
with muscle weakness or episodes of muscle pain and rhabdomyolysis. Cardiomyopathy may be present during acute attacks provoked by fasting. The left ventricle may be hypertrophic or dilated and show some improvement, including normalization of cardiac function. Occurred in several patients, but most who survived the initial episode did so, avoiding fasting stress. Some investigators have suggested that treatment may be necessary to determine whether this is or is not a real disease. Although most individuals with SCAD deficiency remain asymptomatic throughout life, it has been proposed that there is a subset of individuals with SCAD deficiency with severe manifestations, including dysmorphic facial features, feeding difficulties/failure to thrive, metabolic acidosis, ketotic hypoglycemia, lethargy, developmental delay, hypotonia, dystonia, and myopathy.

**Short-Chain Acyl-Coenzyme A Dehydrogenase Deficiency**

A small number of patients with 2 clear null mutations in the short-chain acyl-CoA dehydrogenase (SCAD) gene have been described with variable phenotype. Most individuals classified as being SCAD deficient have polymorphic DNA changes in the SCAD gene; for example, 2 common polymorphisms are G185S and R147W, which are homozygously present in 7% of the population. Some investigators argue that these may be susceptibility changes, which require a second, as yet unknown, genetic mutation to express a clinical phenotype; while others believe that SCAD deficiency is a harmless biochemical condition. This autosomal recessive disorder presents with neonatal hypoglycemia and may have normal levels of ketone bodies. The diagnosis is indicated by elevated levels of butyrylcarnitine (C4-carnitine) on newborn blood spots or plasma and increased excretion of urinary ethylmalonic acid and butyrylglycine. These metabolic abnormalities are most pronounced in patients with null mutations and variably present in patients who are homozygous for the common polymorphisms.

The necessity for treatment in SCAD deficiency has not yet been established. It has been proposed that long-term evaluation of asymptomatic individuals is necessary to determine whether this is or is not a real disease. Although most individuals with SCAD deficiency remain asymptomatic throughout life, it has been proposed that there is a subset of individuals with SCAD deficiency with severe manifestations, including dysmorphic facial features, feeding difficulties/failure to thrive, metabolic acidosis, ketotic hypoglycemia, lethargy, developmental delay, hypotonia, dystonia, and myopathy.

**Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase/Mitochondrial Trifunctional Protein Deficiency**

The LCHAD enzyme is part of a MTP, which also contains 2 other steps in β-oxidation: long-chain enoyl CoA hydratase and long-chain β-ketothiolase. It is a heterotrimeric protein composed of 4 α and 4 β chains that derive from distinct contiguous genes with a common promoter region. In some patients, only the LCHAD activity of the MTP is affected (LCHAD deficiency), whereas others have deficiencies of all 3 activities (MTP deficiency).

Clinical manifestations include attacks of acute hypoketotic hypoglycemia similar to MCAD deficiency; patients often show evidence of more severe disease, including cardiomyopathy, muscle cramps and weakness, and abnormal liver function (cholestasis). Toxic effects of fatty acid metabolites may produce pigmented retinopathy leading to blindness, progressive liver failure, peripheral neuropathy, and rhabdomyolysis. Life-threatening obstetric complications, acute fatty liver of pregnancy, and HELLP syndrome are observed in heterozygous mothers carrying homozygotic fetuses affected with LCHAD/MTP deficiency. Sudden unexpected infant death may occur. The diagnosis is indicated by elevated levels of blood spot or plasma 3-hydroxy acylcarnitines of chain lengths C14-C16. Urinary organic acid profile in patients may show increases in levels of 3-hydroxydicarboxylic acids of chain lengths C6-C14. Secondary carnitine deficiency is common. A common mutation in the α subunit, E474Q, is seen in more than 60% of LCHAD-deficient patients. This mutation in the fetus is especially associated with the obstetric complications, but other mutations in either subunit may also be linked to maternal illness.

Treatment is similar to that for MCAD or VLCAD deficiency; that is, avoiding fasting stress. Some investigators have suggested that dietary supplements with medium-chain triglyceride oil to bypass the defect in long-chain fatty acid oxidation and docosahexaenoic acid (for protection against the retinal changes) may be useful. Liver transplantation has been attempted in cases with severe liver failure, but does not apparently improve survival.
not ameliorate the metabolic abnormalities or prevent the myopathic or retinal complications.

**Short-Chain 3-Hydroxyacyl-Coenzyme A Dehydrogenase Deficiency**

Only 12 patients with proven mutations of short-chain 3-hydroxyacyl-CoA dehydrogenase (SCHAD) have been reported, although a few additional unpublished cases are known to the authors. Most cases with recessive mutations of the SCHAD gene have presented with episodes of hypoketotic hypoglycemia that was caused by hyperinsulinism. In contrast to patients with other forms of fatty acid oxidation disorders, these cases required specific therapy with diazoxide for hyperinsulinism to avoid recurrent hypoglycemia. A single case with compound heterozygous mutations presented with fulminant hepatic failure at age 10 mo. The SCHAD protein has a nonenzymatic function (moonlighting) in which it directly interacts with glutamate dehydrogenase (GDH) to inhibit its activity. In the absence of an SCHAD protein, this inhibition is removed leading to upregulation of GDH enzyme activity, a recognized cause of hyperinsulinism usually caused by activating mutations of the GDH gene. This severe deficiency of SCHAD protein often presents predominantly as protein sensitive hypoglycemia rather than as fasting hypoglycemia. It appears that if a SCHAD protein is present the inhibition of GDH is maintained even when there is no SCHAD enzyme activity; these patients may present with a more traditional fatty acid oxidation defect. Specific metabolic markers for SCHAD deficiency include elevated plasma C4-hydroxy acylcarnitine and urine 3-hydroxyglutaric acid.

Treatment of SCHAD deficient patients with hyperinsulinism is with diazoxide. There is insufficient experience with the non-hyperinsulinemic form of SCHAD deficiency at present to recommend treatment modalities, but prevention of fasting seems advisable, which is similar to other fatty acid oxidation disorders.

**DEFECTS IN THE CARNITINE CYCLE**

**Plasma Membrane Carnitine Transport Defect (Primary Carnitine Deficiency)**

Primary carnitine deficiency is the only genetic defect in which carnitine deficiency is the cause, rather than the consequence, of impaired fatty acid oxidation. The most common presentation is progressive cardiomyopathy with or without skeletal muscle weakness beginning at 1-4 yr of age. A smaller number of patients may present with fasting hypoketotic hypoglycemia in the 1st yr of life before the cardiomypathy becomes symptomatic. The underlying defect involves the plasma membrane sodium gradient-dependent carnitine transporter that is present in heart, muscle, and kidney. This transporter is responsible both for maintaining intracellular carnitine concentrations 20-50-fold higher than plasma concentrations and for renal conservation of carnitine.

Diagnosis of the carnitine transporter defect is aided by the fact that patients have extremely reduced carnitine levels in plasma and muscle (1-2% of normal). Heterozygote parents have plasma carnitine levels approximately 50% of normal. Fasting ketogenesis may be normal because liver carnitine transport is normal, but it may become impaired if dietary carnitine intake is interrupted. The fasting urinary organic acid profile may show a hypoketotic dicarboxylic aciduria pattern if hepatic fatty acid oxidation is impaired, but it is otherwise unremarkable. The defect in carnitine transport can be demonstrated clinically by the severe reduction in renal carnitine threshold or by in vitro assay of carnitine uptake using cultured fibroblasts or lymphoblasts. Mutations in the organic cation/carnitine transporter (OCTN2) underlie this disorder. Treatment with pharmacologic doses of oral carnitine (100-200 mg/kg/day) is highly effective in correcting the cardiomypathy and muscle weakness, as well as any impairment in fasting ketogenesis. Muscle total carnitine concentrations remain <5% of normal on treatment.

**Carnitine Palmitoyltransferase-IA Deficiency**

Several dozen infants and children have been described with a deficiency of the liver and kidney carnitine palmitoyltransferase-I (CPT-I) isozyme (CPT-IA). Clinical manifestations include fasting hypoketotic hypoglycemia, occasionally with markedly abnormal liver function tests and, rarely, with renal tubular acidosis. The heart and skeletal muscle are not involved because the muscle isozyme is unaffected. Fasting urinary organic acid profile sometimes shows a hypo-ketotic C₆-C₁₂ dicarboxylic aciduria but may be normal. Plasma acylcarnitine analysis demonstrates mostly free carnitine with very little acylated carnitine. This observation has been used to establish CPT-IA diagnosis on newborn screening by tandem mass spectrometry. CPT-IA deficiency is the only fatty acid oxidation disorder in which plasma total carnitine levels are elevated often to 150-200% of normal. This may be explained by the fact that the inhibitory effects of long-chain acylcarnitines on the renal tubular carnitine transporter are absent in CPT-IA deficiency. The enzyme defect can be demonstrated in cultured fibroblasts or lymphoblasts. CPT-IA deficiency in the fetus has been associated with acute fatty liver of pregnancy in the mother in a single case report. A common variant in the CPT-IA gene has been identified in individuals of Inuit background in the United States and First Nations tribes in Canada and Greenland. The variant is detected by a positive newborn acylcarnitine screen; enzyme activity is reduced by 80% and regulation by malonyl-CoA is lost. It has not been established if this is a pathologic DNA variant or an adaptation to ancient Inuit and First Nations high-fat diets. This variant is associated with an increased risk for sudden infant death syndrome. Treatment for the severe form of CPT-IA deficiency is similar to that for MCAD deficiency with avoidance of situations where fasting ketogenesis is necessary.

**Carnitine:Acylcarnitine Translocase Deficiency**

This defect of the inner mitochondrial membrane carrier protein for fatty acylcarnitines blocks the entry of long-chain fatty acids into the mitochondria for oxidation. The clinical phenotype of this disorder is characterized by a severe and generalized impairment of fatty acid oxidation. Most newborn patients present with attacks of fasting-induced hypoglycemia, hyperammonemia, and cardiorespiratory collapse. All symptomatic newborns have had evidence of cardiomyopathy and muscle weakness. Several patients with a partial translocase deficiency and milder disease without cardiac involvement have also been identified. No distinctive urinary or plasma organic acids are noted, although increased levels of plasma long-chain acylcarnitines of chain lengths C₁₅-C₁₈ are reported. Diagnosis can be confirmed using genetic analysis. Functional carnitine:acylcarnitine translocase activity can be measured in cultured fibroblasts or lymphoblasts. Treatment is similar to that of other long-chain fatty acid oxidation disorders.

**Carnitine Palmitoyltransferase-II Deficiency**

Three forms of CPT-II deficiency have been described. The severe neonatal lethal presentation of this disorder is associated with a profound enzyme deficiency, and early death has been reported in several newborns with dysplastic kidneys, cerebral malformations, and mild facial anomalies. A milder, second defect, is associated with an adult presentation of episodic rhabdomyolysis. The first episode usually does not occur until late childhood or early adulthood. Attacks may be precipitated by prolonged exercise. There is aching muscle pain and myoglobinuria that may be severe enough to cause renal failure. Serum levels of creatine kinase are elevated to 5,000-100,000 units/L. Fasting hypoglycemia has not been described, but fasting may contribute to attacks of myoglobinuria. Muscle biopsy shows increased deposition of neutral fat. The myopathic presentation of CPT-II deficiency is associated with a common mutation S113L. This mutation produces a heat-labile protein that is unstable to increased muscle temperature during exercise resulting in the myopathic presentation. The third intermediate form of CPT-II deficiency presents in infancy/early childhood with fasting-induced hepatic failure, cardiomyopathy, and skeletal myopathy with hypoketotic hypoglycemia, but does not have the severe developmental changes seen in the neonatal lethal presentation. This pattern is similar to that seen in VLCAD deficiency and management is identical.
Diagnosis of all forms of CPT-II deficiency can be made by a combination of molecular analysis and demonstrating deficient enzyme activity in muscle or other tissues and in cultured fibroblasts.

### DEFECTS IN THE ELECTRON TRANSFER PATHWAY

**Electron Transfer Flavoprotein and Electron Transfer Flavoprotein Dehydrogenase Deficiencies (Glutaric Acidemia Type 2, Multiple Acyl-Coenzyme A Dehydrogenation Defects)**

ETF and ETF-DH function to transfer electrons into the mitochondrial electron transport chain from dehydrogenation reactions catalyzed by VLCAD, MCAD, and SCAD, as well as by glutaryl-CoA dehydrogenase and 4 enzymes involved in branched-chain amino acid oxidation. Deficiencies of ETF or ETF-DH produce illness that combines the features of impaired fatty acid oxidation and impaired oxidation of several amino acids. Complete deficiencies of either protein are associated with severe illness in the newborn period, characterized by acidosis, hypoketotic hypoglycemia, coma, hypotonia, cardiomyopathy, and an unusual odor of sweaty feet caused by isovaleryl-CoA dehydrogenase inhibition. Some affected neonates have had facial dysmorphism and polyhydramnios similar to that seen in severe CPT-II deficiency, which suggests that toxic effects of accumulated metabolites may occur in utero.

Diagnosis can be made from the urinary organic acid profile, which shows abnormalities corresponding to blocks in oxidation of fatty acids (ethylmalonate and C6-C10 dicarboxylic acids), lysine (glutarate), and branched-chain amino acids (isovaleryl-, isobutyryl-, and α-methylbutyryl-glycine) and by molecular testing. Most severely affected infants do not survive the neonatal period.

Partial deficiencies of ETF and ETF-DH produce a disorder that may mimic MCAD deficiency or other milder fatty acid oxidation defects. These patients have attacks of fasting hypoketotic coma. The urinary organic acid profile reveals primarily elevations of dicarboxylic acids and ethylmalonate, derived from short-chain fatty acid intermediates. Secondary carnitine deficiency is present. Some patients with mild forms of ETF/ETF-DH deficiency benefit from treatment with high doses of riboflavin, which is a cofactor for the pathway of electron transfer.

### DEFECTS IN KETONE SYNTHESIS PATHWAY

**β-Hydroxy-β-Methylglutaryl-Coenzyme A Synthase Deficiency**

See Chapter 85.6.

HMG-CoA synthase is the rate-limiting step in the conversion of acetyl-CoA derived from fatty acid β-oxidation in the liver to ketones. Several patients with this defect have recently been identified. The presentation is one of fasting hypoketotic hypoglycemia without evidence of impaired cardiac or skeletal muscle function. Urinary organic acid profile showed only a hypoketotic dicarboxylic aciduria. Plasma and tissue carnitine levels are normal, in contrast to all the other disorders of fatty acid oxidation. A separate synthase enzyme, present in cytosol for cholesterol biosynthesis, is not affected. The HMG-CoA synthase defect is expressed only in the liver and cannot be demonstrated in cultured fibroblasts. The gene has been cloned, and mutations in the affected patients have been characterized. Avoiding fasting is usually a successful treatment.

**β-Hydroxy-β-Methylglutaryl-Coenzyme A Lyase Deficiency**

See Chapter 85.6.

### DEFECTS IN KETONE BODY UTILIZATION

The ketone bodies, β-hydroxybutyrate and acetoacetate, are the end products of hepatic fatty acid oxidation and are important metabolic fuels for the brain during fasting. Two defects in utilization of ketones in brain and other peripheral tissues present as episodes of hyperketotic coma, with or without hypoglycemia.

**Succinyl-Coenzyme A:3-Ketoacid-Coenzyme A Transferase Deficiency**

See Chapter 85.6.

Several patients with succinyl-CoA:3-ketoacid-CoA transferase (SCOT) deficiency have been reported. The characteristic presentation is an infant with recurrent episodes of severe ketoacidosis induced by fasting. Plasma acylcarnitine and urine organic acid abnormalities do not distinguish SCOT deficiency from other causes of ketoacidosis. Treatment of episodes requires infusion of glucose and large amounts of bicarbonate until metabolically stable. Patients usually exhibit inappropriate hyperketonemia even between episodes of illness. SCOT is responsible for activating acetoacetate in peripheral tissues using succinyl-CoA as a donor to form acetoacetoyl-CoA. Deficient enzyme activity can be demonstrated in brain, muscle, and fibroblasts from affected patients. The gene has been cloned, and numerous mutations have been characterized.

**β-Ketothiolase Deficiency**

See Chapter 85.6.

Bibliography is available at Expert Consult.

### 86.2 Disorders of Very Long Chain Fatty Acids

**Gerald V. Raymond**

#### PEROXISOMAL DISORDERS

The peroxisomal diseases are genetically determined disorders caused either by the failure to form or maintain the peroxisome or by a defect in the function of a single protein that is normally located in this organelle. These disorders cause serious disability in childhood and occur more frequently and present a wider range of phenotype than has been recognized in the past.

**Etiology**

Peroxisomal disorders are subdivided into 2 major categories (Table 86-2).

In category A, the peroxisomal biogenesis disorders (PBDs), the basic defect is the failure to import 1 or more proteins into the organelle. In category B, defects affect a single peroxisomal protein. The peroxisome is present in all cells except mature erythrocytes and is a subcellular organelle surrounded by a single membrane; more than 50

<table>
<thead>
<tr>
<th>Table 86-2</th>
<th>Classification of Peroxisomal Disorders</th>
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</thead>
<tbody>
<tr>
<td><strong>A:</strong> DISORDERS OF PEROXISOME IMPORT</td>
<td></td>
</tr>
<tr>
<td>A1: Zellweger syndrome</td>
<td></td>
</tr>
<tr>
<td>A2: Neonatal adrenoleukodystrophy</td>
<td></td>
</tr>
<tr>
<td>A3: Infantile Refsum disease</td>
<td></td>
</tr>
<tr>
<td>A4: Rhizomelic chondrodysplasia punctata</td>
<td></td>
</tr>
<tr>
<td><strong>B:</strong> DEFECTS OF SINGLE PEROXISOMAL ENZYME</td>
<td></td>
</tr>
<tr>
<td>B1: X-linked adrenoleukodystrophy</td>
<td></td>
</tr>
<tr>
<td>B2: Acyl-CoA oxidase deficiency</td>
<td></td>
</tr>
<tr>
<td>B3: Bifunctional enzyme deficiency</td>
<td></td>
</tr>
<tr>
<td>B4: Peroxisomal thiolase deficiency</td>
<td></td>
</tr>
<tr>
<td>B5: Classic Refsum disease</td>
<td></td>
</tr>
<tr>
<td>B6: 2-Methylacyl-CoA racemase deficiency</td>
<td></td>
</tr>
<tr>
<td>B7: DHAP acyltransferase deficiency</td>
<td></td>
</tr>
<tr>
<td>B8: Alkyl-DHAP synthase deficiency</td>
<td></td>
</tr>
<tr>
<td>B9: Mevalonic aciduria</td>
<td></td>
</tr>
<tr>
<td>B10: Glutaric aciduria type III</td>
<td></td>
</tr>
<tr>
<td>B11: Hyperoxaluria type I</td>
<td></td>
</tr>
<tr>
<td>B12: Acatalasemia</td>
<td></td>
</tr>
</tbody>
</table>

CoA, coenzyme A; DHAP, dihydroxyacetone phosphate.
Bibliography


peroxisomal enzymes are identified. Some enzymes are involved in the production and decomposition of hydrogen peroxide; others are concerned with lipid and amino acid metabolism. Most peroxisomal enzymes are first synthesized in their mature form on free polyribosomes and enter the cytoplasm. Proteins that are destined for the peroxisome contain specific peroxisome targeting sequences (PTSs). Most peroxisomal matrix proteins contain PTS1, a 3-amino acid sequence at the carboxyl terminus. PTS2 is an aminoterminal sequence that is critical for the import of enzymes involved in plasmalogen and branched-chain fatty acid metabolism. Import of proteins involves a complex series of reactions that involves at least 23 distinct proteins. These proteins, referred to as peroxins, are encoded by \textit{PEX} genes.

**Epidemiology**

Except for X-linked adrenoleukodystrophy (ALD), all the peroxisomal disorders in Table 86–2 are autosomal recessive traits. ALD is the most common peroxisomal disorder, with an estimated incidence of 1 in 17,000 live births. The combined incidence of the other peroxisomal disorders is estimated to be 1 in 50,000 live births.

**Pathology**

Absence or reduction in the number of peroxisomes is pathognomonic for disorders of peroxisome biogenesis. In most disorders, there are membranous sacs that contain peroxisomal integral membrane proteins, which lack the normal complement of matrix proteins; these are peroxisome “ghosts.” Pathologic changes are observed in most organs and include profound and characteristic defects in neuronal migration; micronodular cirrhosis of the liver; renal cysts; chondrodysplasia punctata; sensorineural hearing loss; retinopathy; congenital heart failure. Table 86–4 lists the main clinical abnormalities.

**Pathogenesis**

It is likely that all pathologic changes are secondary to the peroxisome defect. Multiple peroxisomal enzymes fail to function in the PBDs (Table 86–3). The enzymes that are diminished or absent are synthesized but are degraded abnormally fast because they may be unprotected outside of the peroxisome. It is not clear how defective peroxisome functions lead to the widespread pathologic manifestations.

Mutations in 12 different \textit{PEX} genes have been identified in PBDs. The pattern and severity of pathologic features vary with the nature of the import defects and the degree to which import is impaired. These gene defects lead to disorders that were named before their relationship to the peroxisome was recognized, namely, Zellweger syndrome, neonatal ALD, infantile Refsum disease, and rhizomelic chondrodysplasia punctata (RCDP). The first 3 disorders are considered to form a clinical continuum, with Zellweger syndrome the most severe, infantile Refsum disease the least severe, and neonatal ALD intermediate. They can be caused by mutations in any of the 11 genes involved in peroxisome assembly. The specific gene defects cannot be distinguished on the basis of clinical features. The clinical severity varies with the degree to which protein import is impaired. Mutations that abolish import completely are often associated with the Zellweger syndrome phenotype, whereas a missense mutation, in which some degree of import function is retained, leads to the somewhat milder phenotypes. A defect in \textit{PEX7}, which involves the import of proteins that utilize PTS2, is associated with RCDP. \textit{PEX7} defects that leave import partially intact are associated with milder phenotypes, some of which resemble classic Refsum disease.

The genetic disorders that involve single peroxisomal enzymes usually have clinical manifestations that are more restricted and relate to the single biochemical defect. The primary adrenal insufficiency of ALD is caused by accumulation of very-long-chain fatty acids (VLCFAs) in the adrenal cortex, and the peripheral neuropathy in Refsum disease is caused by the accumulation of phytanic acid in Schwann cells and myelin.

**Peroxisomal Biogenesis Disorders with Milder or Atypical Phenotypes**

Newborn infants with Zellweger syndrome show striking and consistent recognizable abnormalities. Of central diagnostic importance are the typical facial appearance (high forehead, unslanting palpebral fissures, hypoplastic supraorbital ridges, and epicantal folds; Fig. 86–3), severe weakness and hypotonia, neonatal seizures, and eye abnormalities. Because of the hypotonia and craniofacial appearance, Down syndrome may be suspected. Infants with Zellweger syndrome rarely live more than a few months. More than 90% show postnatal growth failure. Table 86–4 lists the main clinical abnormalities.

 Patients with neonatal ALD show fewer, less-prominent craniofacial features. Neonatal seizures occur frequently. Some degree of psychomotor developmental delay is present; function remains in the severely or profoundly retarded range, and development may regress after 3–5 yr of age, probably from a progressive leukodystrophy. Hepatomegaly, impaired liver function, pigmentary degeneration of the retina, and severely impaired hearing are invariably present. Adrenocortical function is usually impaired and may require adrenal hormone replacement. Chondrodysplasia punctata and renal cysts are absent.

<table>
<thead>
<tr>
<th>Table 86-3</th>
<th>Abnormal Laboratory Findings Common to Disorders of Peroxisome Biogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peroxisomes absent to reduced in number</td>
<td></td>
</tr>
<tr>
<td>Catalase in cytosol</td>
<td></td>
</tr>
<tr>
<td>Deficient synthesis and reduced tissue levels of plasmalogens</td>
<td></td>
</tr>
<tr>
<td>Defective oxidation and abnormal accumulation of very-long-chain fatty acids</td>
<td></td>
</tr>
<tr>
<td>Deficient oxidation and age-dependent accumulation of phytanic acid</td>
<td></td>
</tr>
<tr>
<td>Defects in certain steps of bile acid formation and accumulation of bile acid intermediates</td>
<td></td>
</tr>
<tr>
<td>Defects in oxidation and accumulation of L-pipecolic acid</td>
<td></td>
</tr>
<tr>
<td>Increased urinary excretion of dicarboxylic acids</td>
<td></td>
</tr>
</tbody>
</table>

Figure 86–3 Four patients with Zellweger cerebrohepatorenal syndrome. Note the high forehead, epicanthal folds, and hypoplasia of supraorbital ridges and midface. (Courtesy of Hans Zellweger, MD.)
Table 86-4  Main Clinical Abnormalities in Zellweger Syndrome

<table>
<thead>
<tr>
<th>ABNORMAL FEATURE</th>
<th>NO.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>High forehead</td>
<td>58</td>
<td>97</td>
</tr>
<tr>
<td>Flat occiput</td>
<td>13</td>
<td>81</td>
</tr>
<tr>
<td>Large fontanelle(s), wide sutures</td>
<td>55</td>
<td>96</td>
</tr>
<tr>
<td>Shallow orbital ridges</td>
<td>33</td>
<td>100</td>
</tr>
<tr>
<td>Low/broad nasal bridge</td>
<td>23</td>
<td>100</td>
</tr>
<tr>
<td>Epicantus</td>
<td>33</td>
<td>92</td>
</tr>
<tr>
<td>High arched palate</td>
<td>35</td>
<td>95</td>
</tr>
<tr>
<td>External ear deformity</td>
<td>39</td>
<td>97</td>
</tr>
<tr>
<td>Micrognathia</td>
<td>18</td>
<td>100</td>
</tr>
<tr>
<td>Redundant skin fold of neck</td>
<td>13</td>
<td>100</td>
</tr>
<tr>
<td>Brushfield spots</td>
<td>5</td>
<td>83</td>
</tr>
<tr>
<td>Cataract/cloudy cornea</td>
<td>30</td>
<td>86</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>7</td>
<td>58</td>
</tr>
<tr>
<td>Abnormal retinal pigmentation</td>
<td>6</td>
<td>40</td>
</tr>
<tr>
<td>Optic disc pallor</td>
<td>17</td>
<td>74</td>
</tr>
<tr>
<td>Severe hypotonia</td>
<td>94</td>
<td>99</td>
</tr>
<tr>
<td>Abnormal Moro response</td>
<td>26</td>
<td>100</td>
</tr>
<tr>
<td>Hyporeflexia or areflexia</td>
<td>56</td>
<td>98</td>
</tr>
<tr>
<td>Poor sucking</td>
<td>74</td>
<td>96</td>
</tr>
<tr>
<td>Gavage feeding</td>
<td>26</td>
<td>100</td>
</tr>
<tr>
<td>Epileptic seizures</td>
<td>56</td>
<td>92</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td>45</td>
<td>100</td>
</tr>
<tr>
<td>Impaired hearing</td>
<td>9</td>
<td>40</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>30</td>
<td>81</td>
</tr>
</tbody>
</table>


Patients with infantile Refsum disease have survived to adulthood. They are able to walk, although gait may be ataxic and broad based. Cognitive function is in the severely impaired range. All have sensorineural hearing loss and pigmentary degeneration of the retina. They have moderately dysmorphic features that may include epicanthal folds, a flat bridge of the nose, and low-set ears. Early hypotonia and hepatomegaly with impaired function are common. Levels of plasma cholesterol and high- and low-density lipoprotein are often moderately reduced. Chondrodysplasia punctata and renal cortical cysts are absent. Postmortem study in infantile Refsum disease reveals micronodular liver cirrhosis and small hypoplastic adrenals. The brain shows no malformations, except for severe hypoplasia of the cerebellar granule layer and ectopic locations of the Purkinje cells in the molecular layer. The mode of inheritance is autosomal recessive.

Some patients with PBDs have milder and atypical phenotypes. They may present with peripheral neuropathy or with retinopathy, impaired vision, or cataracts in childhood, adolescence, or adulthood and have been diagnosed to have Charcot-Marie-Tooth disease or Usher syndrome. Some patients have survived to the 5th decade. Defects in PEX7, which most commonly lead to the RCDP phenotype, may also lead to a milder phenotype with clinical manifestations similar to those of classical Refsum disease (phytanoyl-CoA hydroxylase deficiency).

Rhizomelic Chondrodysplasia Punctata

RCDP is characterized by the presence of stippled foci of calcification within the hyaline cartilage and is associated with dwarfing, cataracts (72%), and multiple malformations caused by contractures. Vertebral bodies have a coronal cleft filled by cartilage that is a result of an embryonic arrest. Disproportionate short stature affects the proximal parts of the extremities (Fig. 86-4A). Radiologic abnormalities consist of shortening of the proximal limb bones, metaphyseal cupping, and disturbed ossification (Fig. 86-4B). Height, weight, and head circumference are less than the 3rd percentile, and these children have a severe intellectual disability. Skin changes such as those observed in ichthyosiform erythroderma are present in approximately 25% of patients.

Isolated Defects of Peroxisomal Fatty Acid Oxidation

The disorders labeled B1 through B3 (see Table 86-2) each involve 1 of 3 enzymes involved in peroxisomal fatty acid oxidation. Their clinical manifestations resemble those of the Zellweger spectrum disorder continuum; they can be distinguished from disorders of peroxisome biogenesis only by laboratory tests. Defects of bifunctional enzyme are common and are found in approximately 15% of patients with the Zellweger spectrum disorder. Patients with isolated acyl-CoA oxidase deficiency have a somewhat milder phenotype that resembles and come to attention because of the development of a childhood leukodystrophy.

Isolated Defects of Plasmalogen Synthesis

Plasmalogens are lipids in which the first carbon of glycerol is linked to an alcohol rather than a fatty acid. They are synthesized through a complex series of reactions, the first 2 steps of which are catalyzed by the peroxisomal enzymes dihydroxyacetone phosphate alkyll transferase and synthase. Deficiency of either of these enzymes (B4 and B5 in Table 86-2) leads to a phenotype that is clinically indistinguishable from the peroxisomal import disorder RCDP. This latter disorder is caused by a defect in PEX7, the receptor for PEX. It shares the severe deficiency of plasmalogens with disorders B4 and B5 but, in addition, has defects of phytic acid oxidation. The fact that disorders B4 and B5 are associated with the full phenotype of RCDP suggests that a deficiency of plasmalogens is sufficient to produce it.
Classic Refsum Disease
The defective enzyme (phytanyl-CoA oxidase) is localized to the peroxisome. The manifestation of classic adult Refsum disease includes impaired vision from retinitis pigmentosa, ichthyosis, peripheral neuropathy, ataxia, and, occasionally, cardiac arrhythmias. In contrast to infantile Refsum disease, cognitive function is normal and there are no congenital malformations. Classic Refsum disease often does not manifest until young adulthood, but visual disturbances such as night blindness, ichthyosis, and peripheral neuropathy may already be present in childhood and adolescence. Early diagnosis is important because institution of a phytanic acid-restricted diet can reverse the peripheral neuropathy and prevent the progression of the visual and central nervous system manifestations. The classic Refsum disease phenotype may also be caused by defects in PEX7.

2-Methylacyl-Coenzyme A Racemase Deficiency
This disorder is caused by an enzyme defect that leads to the accumulation of the branched-chain fatty acids (phytanic and pristanic acid) and bile acids. Patients present with adult-type peripheral neuropathy and may also have pigmentary degeneration of the retina.

Laboratory Findings
Laboratory tests for peroxisomal disorders can be viewed at 3 levels of complexity.

Level 1: Does the Patient Have a Peroxisomal Disorder?
This can be resolved by noninvasive tests that are generally available (see Table 86–4). Measurement of plasma VLCFA is the most commonly used assay. Whereas plasma VLCFA levels are elevated in many patients with peroxisomal disorders, this is not always the case. The most important exception is RCDP, in which VLCFA levels are normal, but plasma phytanic acid levels are increased and red blood cell plasmalogens levels are reduced. In some other peroxisomal disorders, the biochemical abnormalities are still more restricted. Therefore, a panel of tests is recommended and includes plasma levels of VLCFA and phytanic, pristanic, and pipericolic acids and red blood cell levels of plasmalogens. Tandem mass spectrometry techniques also permit convenient quantitation of bile acids in plasma and urine. This panel of tests can be performed on 2 mL samples of venous blood and permits detection of most peroxisomal disorders. Furthermore, normal results make the presence of the typical peroxisomal disorder unlikely.

Level 2: What Is the Precise Nature of the Peroxisomal Disorder?
Table 86–5 lists the main biochemical abnormalities in the various peroxisomal disorders. When combined with the clinical presentation, the panel of level 1 tests (see above) is often sufficient to identify the precise nature of the defect. Marked reduction of erythrocyte plasmalogens levels combined with elevated plasma phytanic acid permits precise diagnosis in a patient with the clinical features of RCDP. Classic Refsum disease can be diagnosed by demonstration of increased plasma phytanic acid combined with normal or reduced levels of pristanic acid levels, while in D-bifunctional enzyme deficiency and 2-methylacyl-CoA racemase deficiency, the levels of pristanic and phytic acid are both increased. Precise identification of some peroxisomal disorders may require more extensive studies in cultured skin fibroblasts. This may be required for the differentiation of PBDs from defects in bifunctional enzyme. In PBDs, the patient's peroxisomes are absent and catalase is in the soluble fraction, whereas in bifunctional enzyme defect, peroxisomes are present and catalase is in the particulate fraction. Fibroblast studies are required to identify the nature of the molecular defect in PBDs. Whether such specialized studies are clinically warranted depends on individual circumstances. Precise definition of the defect in a proband may improve the precision of prenatal diagnosis in at-risk pregnancies, and it is required for carrier detection. It is also of value in setting prognosis.

Level 3: What Is the Molecular Defect?
Definition of the molecular defect in the proband, which is now offered in several laboratories, is essential for carrier detection and speeds prenatal diagnosis. Characterization of the mutation may be of prognostic value in patients with PEX1 defects. This defect is present in approximately 60% of PBD patients, and about half of the PEX1 defects have the G843D allele, which is associated with a significantly milder phenotype than is found in other mutations.

Diagnosis
There are several noninvasive laboratory tests that permit precise and early diagnosis of peroxisomal disorders (see Table 86–4). The challenge in PBDs is to differentiate them from the large variety of other conditions that can cause hypotonia, seizures, failure to thrive, or dysmorphic features. Experienced clinicians can readily recognize classic Zellweger syndrome by its clinical manifestations. However, more mildly affected PBD patients often do not show the full clinical spectrum of disease and may be identifiable only by laboratory assays. Clinical features that serve as indications for these diagnostic assays include severe intellectual disability; weakness and hypotonia; dysmorphic features; neonatal seizures; retinopathy, glaucoma, or cataracts; hearing deficits; enlarged liver and impaired liver function; and chondrodysplasia punctata. The presence of 1 or more of these abnormalities increases the likelihood of this diagnosis. Atypical milder forms presenting as peripheral neuropathy have also been described.

Some patients with the isolated defects of peroxisomal fatty acid oxidation (group B) resemble those with group A disorders and can be detected by the demonstration of abnormally high levels of VLCFAs. Patients with RCDP must be distinguished from patients with other causes of chondrodysplasia punctata. In addition to warfarin embryopathy and Zellweger syndrome, these disorders include the milder autosomal dominant form of chondrodysplasia punctata (Conradi-Hünermann syndrome), which is characterized by longer survival, absence of severe limb shortening, and usually intact intellect; an X-linked dominant form; and an X-linked recessive form associated with a deletion of the terminal portion of the short arm of the X chromosome. RCDP is suspected clinically because of the shortness of limbs, psychomotor retardation, and ichthyosis. The most decisive laboratory test is the demonstration of abnormally low plasmalogens levels in red blood cells and an impaired capacity to synthesize plasmalogens in cultured skin fibroblasts. These biochemical defects are not present in other types of chondrodysplasia punctata. Chondrodysplasia punctata may also be associated with a defect of 3β-hydroxysteroid-Δ7,Δ5-isomerase, an enzyme involved in biosynthesis of cholesterol.

Complications
Patients with Zellweger cerebrohepatorenal syndrome have multiple disabilities involving muscle tone, swallowing, cardiac abnormalities, liver disease, and seizures. These conditions are treated symptomatically, but the prognosis is poor, and most patients succumb in the first year of life. Patients with RCDP may develop quadripareisis owing to compression at the base of the brain.

Treatment
The most effective therapy is the dietary treatment of classic Refsum disease with a phytic acid-restricted diet.

For patients with the somewhat milder variants of the peroxisome import disorders, success has been achieved with multidisciplinary early intervention, including physical and occupational therapy, hearing aids or cochlear implants, alternative communication, nutrition, and support for the parents. Although most patients continue to function in the severely delayed range, some make significant gains in self-help skills, and several are in stable condition in their teens or even early 20s.

Attempts to mitigate some of the secondary biochemical abnormalities include the oral administration of docosahexaenoic acid. The levels of this substance are greatly reduced in patients with disorders of peroxisome biogenesis and this therapy normalizes the plasma levels of...
### Table 86-5  Peroxisomal Disorders That Involve Fatty Acid Oxidation: Diagnostic Assays

<table>
<thead>
<tr>
<th>Disease</th>
<th>Assay</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zellweger syndrome</td>
<td>Plasma VLCFA</td>
<td>Increased</td>
</tr>
<tr>
<td>Neonatal adrenoleukodystrophy</td>
<td>Plasma Phytanic acid</td>
<td>Age-dependent increase</td>
</tr>
<tr>
<td>Infantile Refsum disease</td>
<td>Plasma Pristanic acid</td>
<td>Age-dependent increase</td>
</tr>
<tr>
<td>RBCs</td>
<td>Plasma Bile acid</td>
<td>Increased</td>
</tr>
<tr>
<td>Fibroblasts</td>
<td>Plasma Plasmalogen levels</td>
<td>Increased, abnormal pattern</td>
</tr>
<tr>
<td></td>
<td>Plasma VLCFA levels</td>
<td>Variously decreased</td>
</tr>
<tr>
<td></td>
<td>Plasma VLCFA oxidation</td>
<td>Increased</td>
</tr>
<tr>
<td></td>
<td>Plasma Plasmalogen synthesis</td>
<td>Decreased</td>
</tr>
<tr>
<td></td>
<td>Plasma Phytanic, pristanic oxidation</td>
<td>Decreased</td>
</tr>
<tr>
<td></td>
<td>Catalase localization</td>
<td>Cytosolic</td>
</tr>
<tr>
<td></td>
<td>Immunocytochemistry Peroxisomes absent</td>
<td>PEX gene mutations</td>
</tr>
<tr>
<td></td>
<td>DNA Complementation between infantile Refsum disease and other peroxisomal disorder (except Zellweger)</td>
<td>fibroblasts</td>
</tr>
</tbody>
</table>

| Rhizomelic chondrodysplasia punctata | Plasma Phytanic acid | Increased |
| RBCs | Plasma Plasmalogen levels | Decreased |
| Fibroblasts | Plasma Plasmalogen levels | Decreased |
| | Plasma Phytanic acid oxidation | Decreased |
| | DNA | PEX7 defect |

| X-linked ALD hemizygote | Plasma VLCFA levels | Increased |
| Fibroblasts | Plasma VLCFA oxidation | Increased |
| | DNA ALDP immunoreactivity | Absent in 70% |
| X-linked ALD heterozygote | Plasma VLCFA levels | Variable increase in 85% of heterozygotes |
| Fibroblasts | ALDP immunoreactivity | Variable increase in 90% of heterozygotes |
| | DNA ABCD1 mutation | Variable decrease |

| Bifunctional enzyme defect | Plasma VLCFA | Increased |
| Fibroblasts | Plasma Phytanic acid | Increased |
| | Plasma Pristanic acid | Increased |
| | Plasma Bile acids | Increased |
| | Plasma VLCFA levels | Increased |
| | Plasma Pristanic acid oxidation | Increased |
| | Catalase localization | Peroxisomal |
| | Enzyme D-bifunctional protein deficiency | |

| Acyl-CoA oxidase deficiency | Plasma VLCFA levels | Increased |
| Fibroblasts | Plasma VLCFA oxidation | Increased |
| | Enzyme Acyl-CoA oxidase defect | |

| 2-Methylacyl-CoA racemase deficiency | Plasma Pristanic acid | Increased |
| Fibroblasts | Plasma Bile acids | Increased |
| | Pristanic acid oxidation | Increased |
| | Enzyme 2-Methylacyl-CoA oxidase defect | |

| Classic Refsum disease | Plasma Phytanic acid | Increased |
| Fibroblasts | Plasma Pristanic acid | Decreased |
| | Enzyme Phytanoyl-CoA deficiency | |

**ALD, adrenoleukodystrophy; ALDP, adrenoleukodystrophy protein; CoA, coenzyme A; RBC, red blood cell; VLCFA, very-long-chain fatty acid.**

Genetic Counseling

All the peroxisomal disorders, except hyperoxaluria type 1, can be diagnosed prenatally in the 1st or 2nd trimester. The tests are similar to those described for postnatal diagnosis (see Table 86-5) and use chorionic villus sampling or amniocytes. Because of the 25% recurrence risk, couples with an affected child must be advised about the availability of prenatal diagnosis. Heterozygotes can be identified in ALD and in those disorders in which the molecular defect has been identified.

ADRENOLEUKODYSTROPHY (X-LINKED)

ALD is a genetically determined disorder associated with the accumulation of saturated VLCFAs and a progressive dysfunction of the adrenal cortex and central and peripheral nervous system white matter.

**Etiology**

The key biochemical abnormality is the tissue accumulation of saturated VLCFAs, with a carbon chain length of 24 or more. Excess hexacosanoic acid (C26:0) is the most striking and characteristic feature. This accumulation of fatty acids is caused by genetically deficient peroxisomal degradation of fatty acid. The gene that is defective (ABCD1) codes for a peroxisomal membrane protein (ALDP, the ALD protein). Most families have a mutation that is "private" (unique to that kindred)

**Genetic Counseling**

Alphabetically, the peroxisomal disorders are also divided into two groups: those with a single enzymatic defect and those with multiple enzymatic defects. In the former group, the only enzyme that is defective is the one responsible for the accumulation of VLCFAs. In the latter group, more than one peroxisomal enzyme is defective, and therefore the accumulation of VLCFAs is compounded. The only way to determine the type of peroxisomal disorder is with the identification of the specific enzyme defect, which is done using the assay described in Table 86-5.

**This substance. Although there were anecdotal reports of clinical improvement, a randomized placebo-controlled study failed to find benefit.**
Defects

understood. unknown way by the excess of VLCFAs. Mitochondrial damage and inflammatory response. The inflammatory response may be cytokine medi-
involvement and nervous system involvement. The severity of the plasma membrane and this may interfere with receptor and other cel-
hyperpigmentation is noted. In most patients with this phenotype, response to ACTH stimulation is present in 85% of patients, and mild intracranial pressure or with unilateral mass lesions. Impaired cortisol capacity.

cortex, which leads to variable and seemingly inconsistent visual
Visual disturbances are often caused by involvement of the cerebral tur-
turbances of vision, ataxia, poor handwriting, seizures, and strabismus. Spatial orientation is often impaired. Other initial symptoms are dis-
attention deficit disorder, and worsening school performance in a child most commonly between the ages of 4 and 8.
ment is usually normal in the first 3-4 yr. The most common initial manifestations are hyperactivity, which is often mistaken for an attention deficit disorder, and worsening school performance in a child who had previously been a good student. Auditory discrimination is often impaired, although tone perception is preserved. This may be evidenced by difficulty in using the telephone and greatly impaired performance on intelligence tests in items that are presented verbally. Spatial orientation is often impaired. Other initial symptoms are disturbances of vision, ataxia, poor handwriting, seizures, and strabismus. Visual disturbances are often caused by involvement of the cerebral cortex, which leads to variable and seemingly inconsistent visual capacity. Seizures occur in nearly all patients and may represent the first manifestation of the disease. Some patients present with increased intracranial pressure or with unilateral mass lesions. Impaired cortisol response to ACTH stimulation is present in 85% of patients, and mild hyperpigmentation is noted. In most patients with this phenotype, adrenal dysfunction is recognized only after the condition is diagnosed because of the cerebral symptoms. Cerebral childhood ALD tends to progress rapidly with increasing spasticity and paralysis, visual and hearing loss, and loss of ability to speak or swallow. The mean interval between the first neurologic symptom and an apparently vegetative state is 1.9 yr. Patients may continue in this apparently vegetative state for 10 yr or more.

Adolescent ALD designates patients who experience neurologic symptoms between the ages of 10 and 21 yr. The manifestations resemble those of childhood cerebral ALD except that progression is slower. Approximately 10% of patients present acutely with status epilepticus, adrenal crisis, acute encephalopathy, or coma.

Adrenomyeloneuropathy first manifests in late adolescence or adulthood as a progressive paraparesis caused by long tract degeneration in the spinal cord. Approximately half of the patients also have involvement of the cerebral white matter.

The “Addison only” phenotype is an important condition. Of male patients with Addison disease, 25% may have the biochemical defect of ALD. Many of these patients have intact neurologic systems, whereas others have subtle neurologic signs. Many acquire adrenomyeloneuropathy in adulthood.
The term “asymptomatic ALD” is applied to persons who have the biochemical defect of ALD but are free of neurologic or endocrin disturbances. Nearly all persons with the gene defect eventually become neurologically symptomatic.
Approximately 50% of female heterozygotes acquire a syndrome that resembles adrenomyeloneuropathy but is milder and of later onset. Adrenal insufficiency and cerebral disease are rare.

Chromosome abnormalities and endocrine dysfunction are common in families affected by ALD. Diagnosis of typical ALD usually requires that the individual have clinical signs and symptoms of ALD and that the diagnosis be confirmed by one of the following tests.

Laboratory and Radiographic Findings

Adrenal crisis, acute encephalopathy, or coma.

Laboratory and Radiographic Findings

Adrenal crisis, acute encephalopathy, or coma.

Laboratory and Radiographic Findings

Adrenal crisis, acute encephalopathy, or coma. Impaired Adrenal Function

More than 85% of patients with the childhood form of ALD have elevated levels of ACTH in plasma and a subnormal rise of cortisol levels in plasma following intravenous injection of 250 μg of ACTH (Cortrosyn).

Diagnosis and Differential Diagnosis

The earliest manifestations of childhood cerebral ALD are difficult to distinguish from the more common attention-deficit disorders or
learning disabilities. Rapid progression, signs of dementia, or difficulty in auditory discrimination suggest ALD. Even in early stages, CT or MRI may show strikingly abnormal changes. Other leukodystrophies or multiple sclerosis may mimic these radiographic findings, although early ALD has more of a predilection for the posterior brain than its mimics. Definitive diagnosis depends on demonstration of VLCFA excess, which occurs only in ALD and the other peroxisomal disorders.

Cerebral forms of ALD may present as increased intracranial pressure and unilateral mass lesions. These have been misdiagnosed as gliomas, even after brain biopsy, and several patients have received radiotherapy before the correct diagnosis was made. Measurement of VLCFA in plasma or brain biopsy specimens is the most reliable differentiating test.

Adolescent or adult cerebral ALD can be confused with psychiatric disorders, dementing disorders, or epilepsy. The first clue to the diagnosis of ALD may be the demonstration of white matter lesions by neuroimaging; assays of VLCFA are confirmatory.

ALD cannot be distinguished clinically from other forms of Addison disease; it is recommended that assays of VLCFA levels be performed in all male patients with Addison disease. ALD patients do not usually have antibodies to adrenal tissue in their plasma.

Complications
An avoidable complication is the occurrence of adrenal insufficiency. The most difficult neurologic problems are those related to bed rest, contracture, coma, and swallowing disturbances. Other complications involve behavioral disturbances and injuries associated with defects of spatial orientation, impaired vision and hearing, and seizures.

Treatment
Corticosteroid replacement for adrenal insufficiency or adrenocortical hypofunction is effective. It may be lifesaving and increase general strength and well-being, but it does not alter the course of the neurologic disability.

Bone Marrow Transplantation
Bone marrow transplantation (BMT) benefits patients who show early evidence of the inflammatory demyelination that is characteristic of the rapidly progressive neurologic disability in boys and adolescents with the cerebral ALD phenotype. BMT is a high-risk procedure, and patients must be selected with great care. The mechanism of the beneficial effect is incompletely understood. Bone marrow-derived cells do express ALDP, the protein that is deficient in ALD; approximately 50% of brain microglial cells are bone marrow derived. The favorable effect may be caused by modification of the brain inflammatory response. Five to 10 yr follow-up of boys and adolescents who had early cerebral involvement has shown stabilization. On the other hand, BMT has not shown favorable effects in patients who already had severe brain involvement and may accelerate disease progression under these circumstances. The nonverbal IQ has been found to be of predictive value, and transplant is not recommended in patients with performance IQ significantly below 80. Unfortunately, in more than half the patients who are diagnosed because of neurologic symptoms, the illness is so advanced at the time of diagnosis that they are not candidates for transplant.

Consideration of BMT is most relevant in neurologically asymptomatic or mildly involved patients. Screening at-risk relatives of symptomatic patients identifies these patients most frequently. Screening by measurement of plasma VLCFA levels in patients with Addison disease may also identify candidates for BMT. Because of its risk (10-20% mortality) and the fact that up to 50% of untreated patients with ALD do not develop inflammatory brain demyelination, transplant is not recommended in patients who are free of demonstrable brain involvement. The MRI is also of key importance for the crucial decision of whether transplant should be performed. MRI abnormalities precede...
clinically evident neurologic or neuropsychologic abnormalities. The brain MRI should be monitored at 6 mo intervals in neurologically asymptomatic boys and adolescents between the ages of 3 and 15 yr. If the MRI is normal, BMT is not indicated. If brain MRI abnormalities develop, the patient should be evaluated at 3 mo intervals to determine if the abnormality is progressive, in combination with careful neurologic and neuropsychologic evaluation; and if early progressive involvement is confirmed, transplant should be considered. Magnetic resonance spectroscopy improves the capacity to determine whether the brain involvement is progressive. It is not known whether BMT has a favorable effect on the noninflammatory spinal cord involvement in adults with the adrenomyeloneuropathy phenotype.

**Lorenzo's Oil Therapy**

The administration of Lorenzo's oil to asymptomatic boys in an open study reduced the risk of developing the childhood cerebral phenotye by a factor of 2 or more. Lorenzo's oil (4:1 mixture of glyceryl trioleate and glyceryl trirucinate) combined with a dietary regimen is under investigation for neurologically asymptomatic boys who have a normal brain MRI and are younger than 8 yr old. It has been determined that it must be supervised carefully. Adrenal function and brain MRI must be monitored. Patients who develop progressive MRI abnormalities are evaluated for hematopoietic stem cell transplant when changes are still in an early phase. Lorenzo's oil has not been shown to alter disease progression in patients who already have cerebral involvement.

**Supportive Therapy**

The progressive behavioral and neurologic disturbances associated with the childhood form of ALD are extremely difficult for the family. ALD patients require the establishment of a comprehensive management program and partnership among the family, physician, visiting nursing staff, school authorities, and counselors. In addition, parent support groups (e.g., United Leukodystrophy Foundation) are often helpful. Communication with school authorities is important because under the provisions of Public Law 94-142, children with ALD qualify for special services as "other health impaired" or "multihandicapped." Depending on the rate of progression of the disease, special needs might range from relatively low-level resource services within a regular school program to home- and hospital-based teaching programs for children who are not mobile.

Management challenges vary with the stage of the illness. The early stages are characterized by subtle changes in affect, behavior, and attention span. Counseling and communication with school authorities are of prime importance. Changes in the sleep–wake cycle can be benefited by the judicious use at night of medications for sleep. As the leukodystrophy progresses, the modulation of muscle tone and support of bulbar muscular function are major concerns. Baclofen in gradually increasing doses (5 mg twice a day to 25 mg 4 times a day) is an effective pharmacologic agent for the treatment of acute episodic painful muscle spasms. Other agents may also be used, with care being taken to monitor the occurrence of side effects and drug interactions. As the leukodystrophy progresses, bulbar muscular control is lost. Although initially this can be managed by changing the diet to soft and pureed foods, most patients eventually require a gastrostomy tube. At least 30% of patients have focal or generalized seizures that usually readily respond to standard anticonvulsant medications.

**Genetic Counseling and Prevention**

Genetic counseling and primary and secondary prevention of ALD are of crucial importance. Extended family screening should be offered to all at-risk relatives of symptomatic patients; one program led to the identification of more than 250 asymptomatic affected males and 1,200 women heterozygous for ALD. The plasma assay permits reliable identification of affected males in whom plasma VLCFA levels are increased already on the day of birth. Identification of asymptomatic males permits institution of steroid replacement therapy when appropriate and prevents the occurrence of adrenal crisis, which may be fatal. Monitoring of brain MRI also permits identification of patients who are candidates for BMT at a stage when this procedure has the greatest chance of success. Plasma VLCFA assay is recommended in all male patients with Addison disease. ALD has been shown to be the cause of adrenal insufficiency in more than 25% of boys with Addison disease of unknown cause. Identification of women heterozygous for ALD is more difficult than that of affected males. Plasma VLCFA levels are normal in 15–20% of heterozygous women, and failure to note this has led to serious errors in genetic counseling. DNA analysis permits accurate identification of carriers, provided that the mutation has been defined in a family member, and is the procedure recommended for the identification of heterozygous women.

Prenatal diagnosis of affected male fetuses can be achieved by measurement of VLCFA levels in cultured amniocytes or chorionic villus cells and by mutation analysis. Whenever a new patient with ALD is identified, a detailed pedigree should be constructed and efforts should be made to identify all at-risk female carriers and affected males. These investigations should be accompanied by careful and sympathetic attention to social, emotional, and ethical issues during counseling.

**Bibliography** is available at Expert Consult.

86.3 Disorders of Lipoprotein Metabolism and Transport

*William A. Neal and Collin C. John*

**Epidemiology of Blood Lipids and Cardiovascular Disease**

The Seven Countries Study of geographic, social class, and ethnic differences in coronary heart disease (CHD) around the world found strong associations between average intake of saturated fats, plasma cholesterol, and mortality from CHD. Of all common chronic diseases, none is so clearly influenced by both environmental and genetic factors as CHD. This multifactorial disorder is strongly associated with increasing age and male gender, though it is increasingly apparent that heart disease is underrecognized in women. Tobacco use confers a 2-fold higher lifetime risk. Sedentary activity and high intake of saturated fats leading to adiposity increase risk through differences in the plasma levels of lipoproteins that are atherogenic. Family history is a reflection of the combined influence of lifestyle and genetic predisposition to early heart disease. Risk of premature heart disease associated with positive family history is 1.7 times higher than in families with no such history.

The pathogenesis of atherosclerosis begins during childhood. The Johns Hopkins Precursors Study demonstrated that white male medical students with blood cholesterol levels in the lowest quartile showed only a 10% incidence of CHD 3 decades later, whereas those in the highest quartile had a 40% incidence. The Pathobiological Determinants of Atherosclerosis in Youth Study demonstrated a significant relationship between the weight of the abdominal fat pad and the extent of atherosclerosis found at autopsy on subjects 15-34 yr of age. The Bogalusa Heart Study of more than 3,000 black and white children and adolescents has provided the most comprehensive longitudinal data relating the presence and severity of CHD risk factors with semi-quantifiable severity of atherosclerosis. Coronary atherosclerosis was present in 8.5% of military autopsies performed following combat or unintentional injuries.

The "fetal origins hypothesis" is based on the observation that infants born with low birthweight have a higher incidence of heart disease as adults. Epidemiologic studies support the idea that prenatal and early postnatal conditions may affect adult health status. Children who are large for gestational age at birth and exposed to an intruterine environment of either diabetes or maternal obesity are at increased risk of eventually developing the "metabolic syndrome" (insulin resistance, type II diabetes, obesity, CHD). Breastfeeding preterm infants confers a long-term cardioprotective benefit 13-16 yr later. Those adolescents who were breastfed as infants had lower C-reactive protein
**Bibliography**

**Peroxisomal Disorders**


**Adrenoleukodystrophy (X-Linked)**


concentrations and a 14% lower low-density lipoprotein (LDL):high-density lipoprotein (HDL) ratio compared to those fed infant formulas. The impact of early nutrition and other lifestyle variables on gene expression, known as epigenetics, is an important mechanism by which adult metabolism and body composition may be determined.

In addition, secondary causes of hyperlipidemia may be the result of drugs (cyclosporine, steroids, isotretinoin, protease inhibitors, alcohol, thiazide diuretics, β-blocking agents, valproate) or various diseases (nephrotic syndrome, hypothyroidism, Cushing syndrome, anorexia nervosa, obstructive jaundice).

**BLOOD LIPIDS ANDATHEROGENESIS**

Numerous epidemiologic studies demonstrate the association of hypercholesterolemia, referring to elevated total blood cholesterol, with atherosclerotic disease. The ability to measure subcomponents within classes of lipid particles, as well as markers of inflammation, have further elucidated the process of atherogenesis and plaque rupture leading to acute coronary syndromes. Atherosclerosis affects primarily the coronary arteries but may also involve the aorta, arteries of the lower extremities, and carotid arteries.

The early stage of development of atherosclerosis is thought to begin with vascular endothelial dysfunction and intima-media thickness, which has been shown to occur in preadolescent children with risk factors such as obesity or familial hypercholesterolemia. The complex process of penetration of the intimal lining of the vessel may be a consequence of a variety of insults, including the presence of highly toxic oxidized LDL particles. Lymphocytes and monocytes penetrate the damaged endothelial lining, where they become macrophages laden with LDL lipids and then become foam cells. Such accumulation is counterbalanced by HDL particles capable of removing lipid deposits from the vessel wall. Fundamental to plaque formation is an inflammatory process (elevated C-reactive protein) involving macrophages and the arterial wall. The deposition of lipid within the subendothelial lining of the arterial wall appears macroscopically as fatty streaks, which may to some degree be reversible. A later stage of plaque development involves disruption of arterial smooth muscle cells stimulated by the release of tissue cytokines and growth factors. The atheroma is composed of a core of fatty substance separated from the lumen by collagen and smooth muscle (Fig. 86-6). Growth of the atherosclerotic plaque may result in ischemia of the tissue supplied by the artery. Chronic inflammation within the atheroma, results in plaque instability and subsequent rupture. Platelet adherence leads to clot formation at the site of rupture, resulting in myocardial infarction or a cerebrovascular event.

**PLASMA LIPOPROTEIN METABOLISM AND TRANSPORT**

Abnormalities of lipoprotein metabolism are associated with diabetes mellitus and premature atherosclerosis. Lipoproteins are soluble complexes of lipids and proteins that effect transport of fat absorbed from the diet, or synthesis by the liver and adipose tissues, for utilization and storage. Dietary fat is transported from the small intestine as chylomicrons. Lipids synthesized by the liver as very-low-density lipoproteins (VLDLs) are catabolized to intermediatedensity lipoproteins (IDLs) and LDLs. HDLs are fundamentally involved in VLDL and chylomicron metabolism and cholesterol transport. Nonesterified free fatty acids are metabolically active lipids derived from lipolysis of triglycerides stored in adipose tissue bound to albumin for circulation in the plasma (Fig. 86-7).

Lipoproteins consist of a central core of triglycerides and cholesteryl esters surrounded by phospholipids, cholesterol, and proteins (Fig. 86-8). The density of the several classes of lipoproteins is inversely proportional to the ratio of lipid to protein (Fig. 86-9). Lipoproteins consist of a central core of triglycerides and cholesteryl esters surrounded by phospholipids, cholesterol, and proteins.

Constituent proteins are known as apolipoproteins (Table 86-6). They are responsible for a variety of metabolic functions in addition to their structural role, including cofactors or inhibitors of enzymatic pathways, and mediators of lipoprotein binding to cell surface receptors. ApoA is the major apolipoprotein (Apo) of HDL. ApoB is present in LDL, VLDL, IDL, and chylomicrons. ApoB-100 is derived from the liver, whereas apoB-48 comes from the small intestine. ApoC-I, C-II, and C-III are small peptides important in triglyceride metabolism. Loss of function and disruptive mutations of the APOC3 gene are associated with low levels of triglycerides and a reduced risk of ischemic CHD. Likewise, apoE, which is present in VLDL, HDL, chylomicrons, and chylomicron remnants, plays an important role in the clearance of triglycerides.

**Transport of Exogenous (Dietary) Lipids**

All dietary fat with the exception of medium-chain triglycerides is efficiently carried into the circulation by way of lymphatic drainage from the intestinal mucosa. Triglyceride and cholesteryl esters combine with apoA and apoB-48 in the intestinal mucosa to form chylomicrons, which are carried into the peripheral circulation via the lymphatic system. HDL particles contribute apoC-II to the chylomicrons, required for the activation of lipoprotein lipase (LPL) within the capillary endothelium of adipose, heart, and skeletal muscle tissue. Free fatty acids are oxidized, esterified for storage as

**Figure 86-6** The early stage of development of atherosclerosis begins with penetration of the intimal lining of the vessel by inflammatory cells. Deposition of lipid within the subendothelial lining of the arterial wall eventually leads to disruption of smooth muscle cells to form an atheromatous lipid core that impinges on the lumen. Chronic inflammation leads to plaque instability, setting the stage for plaque rupture and complete occlusion of the vessel lumen by clot formation.
Transport of Endogenous Lipids from the Liver

The formation and secretion of VLDL from the liver and its catabolism to IDL and LDL particles describe the endogenous lipoprotein pathway. Fatty acids used in the hepatic formation of VLDL are derived primarily by uptake from the circulation. VLDL appears to be transported from the liver as rapidly as it is synthesized, and it consists of triglycerides, cholesteryl esters, phospholipids, and apoB-100. Nascent VLDL particles of VLDL secreted into the circulation combine with apoC and apoE. The size of the VLDL particle is determined by the amount of triglyceride present, progressively shrinking in size as triglyceride is hydrolyzed by the action of LPL, yielding free fatty acids for utilization.
or storage in muscle and adipose tissue. Hydrolysis of approximately 80% of the triglyceride present in VLDL particles produces IDL particles containing an equal amount of cholesterol and triglyceride. The remaining remnant IDL is converted to LDL for delivery to peripheral tissues or to the liver. ApoE is attached to the remnant IDL particle to allow binding to the cell and subsequent incorporation into the lysosome. Individuals with deficiency of either apoE2 or heparic triglyceride lipase accumulate IDL in the plasma.

LDL particles account for approximately 70% of the plasma cholesterol in normal individuals. LDL receptors are present on the surfaces of nearly all cells. Most LDL is taken up by the liver, and the rest is transported to peripheral tissues such as the adrenal glands and gonads for steroid synthesis. Dyslipidemia is greatly influenced by LDL-R activity. The efficiency with which VLDL is converted into LDL is also important in lipid homeostasis.

**High-Density Lipoprotein and Reverse Cholesterol Transport**

As hepatic secretion of lipid particles into the bile is the only mechanism by which cholesterol can be removed from the body, transport of excess cholesterol from the peripheral cells is a vitally important function of HDL. HDL is heavily laden with apoA-I containing lipoproteins, which is nonatherogenic in contrast to B lipoproteins. Cholesterol-poor nascent HDL particles secreted by the liver and small intestine are esterified to more mature HDL-2 particles by the action of the enzyme lecithin-cholesterol acyltransferase (LCAT), which facilitates movement of chylomicrons and VLDL into the HDL core. HDL-2 may transfer cholesteryl esters back to apoB lipoproteins mediated by cholesteryl ester transfer protein (CETP), or the cholesteryl-rich particle may be removed from the plasma by endocytosis, completing reverse cholesterol transport. Low HDL may be genetic (deficiency of apoA-I) or secondary to increased plasma triglyceride. LCAT deficiency results in diminished maturation of HDL particles, affecting their ability to do reverse cholesterol transport. This reduces its protective effect on atherosclerosis. There are rare reports, however, of less-than-expected severity of atherosclerosis despite low HDL secondary to LCAT deficiency, suggesting that the relationship may, for unknown reasons, be variable.

**HYPERLIPOPROTEINEMIAS**

**Hypercholesterolemia**

See Table 86-7.

**Familial Hypercholesterolemia**

Familial hypercholesterolemia (FH) is a monogenic autosomal codominant disorder characterized by strikingly elevated LDL cholesterol, premature cardiovascular disease (CVD), and tendon xanthomas. In the past, FH referred to defects of LDL receptor activity. However, genetic studies have broadened our understanding of the etiology of this lipoprotein abnormality to include defects in the genes for ApoB, as well as prpotein convertase subtilisin/kexin type 9. Severe hypercholesterolemia predisposing to premature CHD may be caused by other genetic abnormalities yet to be discovered. Of the nearly 800 mutations described, some result in failure of synthesis of the LDL receptor (receptor negative) and others cause defective binding or release at the lipoprotein-receptor interface. Receptor negative mutations result in more severe phenotypes than receptor defective mutations.

**Homozgyous Familial Hypercholesterolemia**

FH homozygotes inherit 2 abnormal LDL receptor genes, resulting in markedly elevated plasma cholesterol levels ranging between 500 and 1,200 mg/dL. Triglyceride levels are normal to mildly elevated, and HDL levels may be slightly decreased. The condition occurs in 1 in 1,000,000 persons. Receptor-negative patients have <2% normal LDL receptor activity, whereas those who are receptor-defective may have as much as 25% normal activity and a better prognosis.

The prognosis is poor regardless of the specific LDL receptor aberration. Severe atherosclerosis involving the aortic root and coronary arteries is present by early to mid-childhood. These children usually present with xanthomas, which may cause thickening of the Achilles tendon or extensor tendons of the hands, or cutaneous lesions on the hands, elbows, knees, or buttocks (Figs. 86-10, 86-11, and 86-12). Corneal arcus may be present. Family history is informative because premature heart disease is strongly prevalent among relatives of both parents. The diagnosis may be confirmed by measuring LDL receptor activity in cultured skin fibroblasts. Phenotypic expression of the disease may also be assessed by measuring receptor activity on the surface of lymphocytes by using cell sorting techniques.

Untreated homozygous patients rarely survive to adulthood. Symptoms of coronary insufficiency may occur; sudden death is common. LDL apheresis to selectively remove LDL particles from the circulation is recommended for many children as it slows the progression of atherosclerosis. Liver transplantation is also successful in decreasing LDL cholesterol levels, but complications related to immunosuppression are common. HMG-CoA reductase inhibitors may be modestly effective depending on the specific class of LDL receptor defect present. Combination therapy with ezetimibe, selectively blocking cholesterol adsorption in the gut, usually results in further decline in LDL levels; it has largely replaced the use of bile acid sequestrants. Early clinical trials using microsomal triglyceride transfer protein inhibition with lomitapide resulted in a significant reduction in all apoB lipoproteins, including LDL, but hepatic fat deposition as a side effect limits consideration of this pharmacologic approach at this time. Mipomersen, an antisense oligonucleotide that binds to the sequence that encodes apolipoprotein B, reduces the synthesis of apoB and thus also VLDL and LDL; LDL cholesterol levels may decline approximately 25% with this treatment. Adverse effects include flu-like symptoms, hepatic steatosis, and cirrhosis.
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Table 86-7 Hyperlipoproteinemias

<table>
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<th>DISORDER</th>
<th>LIPOPROTEINS ELEVATED</th>
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</tr>
<tr>
<td>Familial dysbetalipoproteinemia</td>
<td>LDL, TG</td>
<td>Tuberoeruptive xanthomas, peripheral vascular disease</td>
<td>AD</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td>Familial chylomicronemia (Frederickson type I)</td>
<td>TG↑↑</td>
<td>Eruptive xanthomas, hepatosplenomegaly, pancreatitis</td>
<td>AR</td>
<td>1 in 1,000,000</td>
</tr>
<tr>
<td>Familial hypertriglyceridemia (Frederickson type IV)</td>
<td>TG↑</td>
<td>CHD</td>
<td>AD</td>
<td>1 in 500</td>
</tr>
<tr>
<td>Familial hypertriglyceridemia (Frederickson type V)</td>
<td>TG↑↑</td>
<td>Choroidal xanthomas ± CHD</td>
<td>AD</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td>Familial hepatic lipase deficiency</td>
<td>VLDL</td>
<td>CHD</td>
<td>AR</td>
<td>&lt;1 in 1,000,000</td>
</tr>
</tbody>
</table>

AD, autosomal dominant; AR, autosomal recessive; CHD, coronary heart disease; LDL, low-density lipoproteins; TG, triglycerides; VLDL, very-low-density lipoproteins.

Figure 86-10 Homozygous familial hypercholesterolemia. Tendon xanthomas in a 5 yr old male with homozygous familial hypercholesterolemia noted at the knee (A), wrist (B), and Achilles (C). (Modified from Macchiaiolo M, Gagliardi MG, Toscano A, et al: Homozygous familial hypercholesterolaemia. Lancet 379:1330, 2012.)

Figure 86-12 Eruptive xanthomata on extensor surface of forearm. (From Durrington P: Dyslipidaemia, Lancet 362:717–731, 2003.)

Figure 86-11 Striate palmar xanthomata. (From Durrington P: Dyslipidaemia, Lancet 362:717–731, 2003.)
Heterozygous Familial Hypercholesterolemia

Heterozygous FH is one of the most common single-gene mutations associated with acute coronary syndromes and atherosclerotic CHD in adults. Its prevalence is approximately 1 in 500 individuals worldwide, but the frequency may be as high as 1 in 250 in selected populations, such as French-Canadians, Afrikaners, and Christian Lebanese, as a result of the founder effect of unique new mutations.

Heart disease accounts for more than half of all deaths in Western society. The pathogenesis of CHD is both environmental and genetic, and the complex interrelationship between the two determines the phenotypic expression of disease. Chinese people with heterozygous FH living in China have a mean LDL cholesterol of 168 mg/dL, whereas immigrant Chinese with the disease living in Canada average 288 mg/dL. This dramatic disparity in lipoprotein levels between geographic locations is expected to narrow as dietary and physical activity practices in China approximate those of the industrialized West.

Because heterozygous FH is a codominant condition with nearly full penetrance, 50% of first-degree relatives of affected individuals will have the disease, as will 25% of 2nd-degree relatives. An estimated 10 million people have FH worldwide. Symptoms of CHD usually occur at the mean age of 45-48 yr in males, and a decade later in females. Genetic testing of individuals who fulfill clinical criteria for the diagnosis of heterozygous FH is positive approximately 80% of the time.

The World Health Organization has targeted FH for individualized intervention strategies because of its large effect on morbidity and mortality. A relatively small percentage of the population accounts for a disproportionately high share of the burden of CVD. The clinical expression of the disease is straightforward and treatment is effective.

One cannot overemphasize the importance of family history for suspecting the possibility of FH. Indeed, the whole basis for deciding which children should have blood cholesterol testing is determined by a family history of premature CHD and/or parental hypercholesterolemia. In fact, the risk of CHD in individuals with FH can be as high as 20 times greater than the general population.

Plasma levels of LDL cholesterol do not allow unequivocal diagnosis of FH heterozygotes, but values are generally twice normal for age because of 1 absent or dysfunctional allele. The U.S. MED-PED (“make early diagnosis–prevent early death”) Program based in Utah has formulated diagnostic criteria. Similar criteria with minor variations exist in the United Kingdom and Holland. Within well-defined FH families, the diagnosis is reliably made according to LDL cutoff points. More stringent criteria are required to establish the diagnosis in previously undiagnosed families, requiring strong evidence of an autosomal inheritance pattern and higher LDL cutoff points. At a total cholesterol level of 310 mg/dL, only 4% of persons in the general population would have FH, whereas 95% of persons who were first-degree relatives of known cases would have the disease. The mathematical probability of FH, verified by molecular genetics, is derived from a U.S. population cohort and may not be applicable to other countries.

Very high cholesterol levels in children should prompt extensive screening of adult 1st- and 2nd-degree relatives (“reverse” cholesterol screening). A child younger than age 18 yr with total plasma cholesterol of 270 mg/dL and/or low-density lipoprotein-cholesterol (LDL-C) of 200 mg/dL has an 88% chance of having FH. Formal clinical diagnosis of FH is based upon the presence of 2 or more family members having elevated LDL cholesterol levels greater than 220 mg/dL. It should be noted, however, that LDL-C level cutoff points vary with age (Table 86-8). Conversely, criteria for diagnosing probable FH in a child whose first-degree relative has known FH require only modest elevation of total cholesterol to 220 mg/dL (LDL-C 155 mg/dL).

Treatment of children with FH should begin with a rather rigorous low-fat diet (see below). Diet alone is rarely sufficient for decreasing blood cholesterol levels to acceptable levels (LDL-C <130 mg/dL).

Ezetimibe blocks cholesterol adsorption in the gastrointestinal tract and has a low risk of side effects. Data suggest that ezetimibe will lower total cholesterol by 20-30 mg/dL. HMG-CoA reductase inhibitors are the drug of choice for treatment of FH because of their remarkable effectiveness and acceptable risk profile. There is sufficient clinical experience with this class of drugs in children to document that they are as effective in children as in adults, and the risks of elevated hepatic enzymes and myositis are no greater than in adults.

Familial Defective ApoB-100

Familial defective apoB-100 is an autosomal dominant condition that is indistinguishable from heterozygous FH. LDL cholesterol levels are increased, triglycerides are normal, adults often develop tendon

*Table 86-8 Percentage of Youths Younger Than Age 18 Yr Expected to Have FH According to Cholesterol Levels and Closest Relative with FH*

<table>
<thead>
<tr>
<th>TOTAL CHOL (mg/dL)</th>
<th>LDL CHOL (mg/dL)</th>
<th>Degree of Relative</th>
<th>Percentage With FH at That Level</th>
<th>GENERAL POPULATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>180</td>
<td>122</td>
<td>7.2</td>
<td>2.4</td>
<td>0.9</td>
</tr>
<tr>
<td>190</td>
<td>130</td>
<td>13.5</td>
<td>5.0</td>
<td>2.2</td>
</tr>
<tr>
<td>200</td>
<td>138</td>
<td>26.4</td>
<td>10.7</td>
<td>4.9</td>
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<tr>
<td>210</td>
<td>147</td>
<td>48.1</td>
<td>23.6</td>
<td>11.7</td>
</tr>
<tr>
<td>220</td>
<td>155</td>
<td>73.1</td>
<td>47.5</td>
<td>27.9</td>
</tr>
<tr>
<td>230</td>
<td>164</td>
<td>90.0</td>
<td>75.0</td>
<td>56.2</td>
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<tr>
<td>240</td>
<td>172</td>
<td>97.1</td>
<td>93.7</td>
<td>82.8</td>
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<td>250</td>
<td>181</td>
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<td>95.3</td>
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<td>260</td>
<td>190</td>
<td>99.9</td>
<td>99.5</td>
<td>99.0</td>
</tr>
<tr>
<td>270</td>
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<td>99.8</td>
</tr>
<tr>
<td>280</td>
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<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>290</td>
<td>220</td>
<td>100.0</td>
<td>100.0</td>
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<tr>
<td>300</td>
<td>230</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Chol, cholesterol; FH, familial hypercholesterolemia; LDL, low-density lipoprotein.

xanthomas, and premature CHD occurs. Familial defective apoB-100 is caused by mutation in the receptor binding region of apoB-100, the ligand of the LDL receptor, with an estimated frequency of 1 in 700 people in Western cultures. It is usually caused by substitution of glutamine for arginine in position 3500 in apoB-100, which results in reduced ability of the LDL receptor to bind LDL cholesterol, thus impairing its removal from the circulation. Specialized laboratory testing can distinguish familial defective apoB-100 from FH, but this is not necessary, except in research settings, because treatment is the same.

**Autosomal Recessive Hypercholesterolemia**

This rare condition, caused by a defect in LDL receptor-mediated endocytosis in the liver, clinically presents with severe hypercholesterolemia at levels intermediate between those found in homozygous and heterozygous FH. It is disproportionately present among Sardinians, and is modestly responsive to treatment with HMG-CoA reductase inhibitors.

**Sitosterolemia**

A rare autosomal recessive condition characterized by excessive intestinal adsorption of plant sterols, sitosterolemia is caused by mutations in the adenosine triphosphate-binding cassette transporter system, which is responsible for limiting adsorption of plant sterols in the small intestine and promotes biliary excretion of the small amounts adsorbed. Plasma cholesterol levels may be severely elevated, resulting in tendon xanthomas and premature atherosclerosis. Diagnosis can be confirmed by measuring elevated plasma sitosterol levels. Treatment with HMG-CoA reductase inhibitors is not effective, but cholesterol adsorption inhibitors, such as ezetimibe, and bile acid sequestrants are effective.

**Polygenic Hypercholesterolemia**

Primary elevation in LDL cholesterol among children and adults is most often polygenic; the small effects of many genes are impacted by environmental influences (diet). Plasma cholesterol levels are modestly elevated; triglyceride levels are normal. Polygenic hypercholesterolemia aggregates in families sharing a common lifestyle but does not follow predictable hereditary patterns found in single-gene lipoprotein defects. Treatment of children with polygenic hypercholesterolemia is directed toward adoption of a healthy lifestyle: reduced total and saturated fat consumption and at least 1 hr of physical activity daily. Cholesterol-lowering medication is rarely necessary.

**Hypercholesterolemia with Hypertriglyceridemia**

**Familial Combined Hyperlipidemia**

This is an autosomal dominant condition characterized by moderate elevation in plasma LDL cholesterol and triglycerides, and reduced plasma HDL cholesterol. It is the most common primary lipid disorder, occurring in approximately 1/200 people. Family history of premature heart disease is typically positive; the formal diagnosis requires that at least two first-degree relatives have evidence of one of three variants of dyslipidemia: (1) >90th percentile plasma LDL cholesterol; (2) >90th percentile LDL cholesterol and triglycerides; and (3) >90th percentile triglycerides. Individuals switch from one phenotype to another. Xanthomas are not a feature of familial combined hyperlipidemia (FCHL). Elevated plasma apoB levels with increased small dense LDL particles support the diagnosis.

Children and adults with FCHL have coexisting adiposity, hypertension, and hyperinsulinemia, suggesting the presence of the metabolic syndrome. Formal diagnosis in adults of this syndrome as defined by the National Cholesterol Education Program (NCEP’s) Adult Treatment Panel III identifies 6 major components: abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance with or without impaired glucose tolerance, evidence of vascular inflammation, and prothrombotic state. It is estimated that 30% of overweight adults fulfill criteria for the diagnosis of metabolic syndrome, including 65% of those with FCHL. Hispanics and South Asians from the Indian subcontinent are especially susceptible. There is no official definition of metabolic syndrome for children. Absolute cutoffs for diagnosis in children do not account for continuous variables in aging, sexual maturation, and race/ethnicity.

FCHL and type II diabetes share many features of the metabolic syndrome, suggesting that they are less distinct entities than originally conceptualized. Genetic association studies reveal evidence for a common genetic background. The resultant metabolic overlap is associated with ectopic fat accumulation and insulin resistance. The mechanisms associating visceral adiposity with the metabolic syndrome and type II diabetes are not fully understood. A plausible unifying principle is that obesity causes endoplasmic reticulum stress, leading to suppression of insulin receptor signaling and thus insulin resistance and heightened inflammatory response. How this relates to atherogenesis is unclear. It is assumed that hypercholesterolemia and, with less certainty, hypertriglyceridemia confer risk for CVD in patients with FCHL. When features of the metabolic syndrome are included in logistic models shared etiologic features such as increased visceral adiposity become apparent. Visceral adiposity increases with age and its importance in children as a risk factor for heart disease and diabetes is limited by the relative paucity of data. Although longitudinal measurement of waist circumference and the presence of intraabdominal fat as determined by MRI is being conducted in the research setting, body mass index (BMI) remains the surrogate for adiposity in the pediatric clinical setting.

The metabolic syndrome is a dramatic illustration of the interaction of genetics and the environment. Genetic susceptibility is essential as an explanation for premature heart disease in individuals with FCHL. Unhealthy lifestyle, poor diet, and physical inactivity contribute to obesity and attendant features of the metabolic syndrome.

The cornerstone of management is lifestyle modification. This includes a diet low in saturated fats, trans fats, and cholesterol, as well as reduced consumption of simple sugars. Increased dietary intake of fruits and vegetables is important, as is 1 hr of moderate physical activity daily. Compliance among children and their parents is often a problem, but small incremental steps are more likely to succeed than aggressive weight-loss strategies. It is very important that the child’s caregivers participate in the process. Plasma triglyceride levels are usually quite responsive to dietary restriction, especially reduction in the amount of sweetened drinks consumed. Blood cholesterol levels may decrease by 10-15%, but if LDL cholesterol remains >160 mg/dL, drug therapy should be considered.

**Familial Dysbetalipoproteinemia (Type III Hyperlipoproteinemia)**

Familial dysbetalipoproteinemia (FDBL) is caused by mutations in the gene for apoE, which when exposed to environmental influences such as high fat, high caloric diet, or excessive alcohol intake, results in a mixed type of hyperlipidemia. Patients tend to have elevated plasma cholesterol and triglycerides to a relatively similar degree. HDL cholesterol is typically normal in contrast to other causes of hypertriglyceridemia associated with low HDL. This rare disorder affects approximately 1 in 10,000 persons. ApoE mediates removal of chylomicron and VLDL remnants from the circulation by binding to hepatic surface receptors. The polymorphic apoE gene expresses in 3 isoforms: apoE3, apoE2, and apoE4. E4 is the “normal” allele present in the majority of the population. The apoE2 isoform has lower affinity for the LDL receptor and its frequency is approximately 7%. Approximately 1% of the population is homozygous for apoE2/E2, the most common mutation associated with FDBL, but only a minority expresses the disease. Expression requires precipitating illnesses such as diabetes, obesity, renal disease, or hypothyroidism. Individuals homozygous for apoE4/E4 are at risk for late-onset Alzheimer disease and dementia from repeated sports-related head injuries.

Most patients with FDBL present in adulthood with distinctive xanthomas. Tuberoeruptive xanthomas resemble small grape-like clusters on the knees, buttoks, and elbows. Prominent orange-yellow discoloration of the creases of the hands (palmar xanthomas) is also typically present. Atherosclerosis, often presenting with peripheral vascular
Hypertriglycerideremias

The familial disorders of triglyceride-rich lipoproteins include both common and rare variants of the Frederickson classification system. These include chylomicronemia (type I), familial hypertriglycerideremia (type IV), and the more severe combined hypertriglycerideremia and chylomicronemia (type V). Hepatic lipase deficiency also results in a similar combined hyperlipidemia.

Familial Chylomicronemia (Type I Hyperlipidemia)

This rare single-gene defect, like FH, is caused by mutations affecting clearance of apoB-containing lipoproteins. Deficiency or absence of LPL or its cofactor apoC-II, which facilitates lipolysis by LPL, causes severe elevation of triglyceride rich plasma chylomicrons. HDL cholesterol levels are decreased. As clearance of these particles is markedly delayed, the plasma is noted to have a turbid appearance even after prolonged fasting (Fig. 86-13). Chylomicronemia caused by LPL deficiency is associated with modest elevation in triglycerides, whereas this is not the case when the cause is deficient or absent apoC-II. Both are autosomal recessive conditions with a frequency of approximately 1 in 1,000,000. The disease usually presents during childhood with acute pancreatitis. Eruptive xanthomas on the arms, knees, and buttocks may be present, and there may be hepatosplenomegaly. The diagnosis is established by assaying triglyceride lipolytic activity. Treatment of chylomicronemia is by vigorous dietary fat restriction supplemented by fat-soluble vitamins. Medium-chain triglycerides that are adsorbed into the portal venous system may augment total fat intake, and administration of fish oils may also be beneficial.

Familial Hypertriglycerideremia (Type IV Hyperlipidemia)

Familial hypertriglycerideremia (FHTG) is an autosomal dominant disorder of unknown etiology that occurs in approximately 1 in 500 individuals. It is characterized by elevation of plasma triglycerides >90th percentile (250-1,000 mg/dL range), often accompanied by slight elevation in plasma cholesterol and low HDL. FHTG does not usually manifest until adulthood, although it is expressed in approximately 20% of affected children. In contrast to FCHL, FHTG is not thought to be highly atherogenic. It is most likely caused by defective breakdown of VLDL, or less often by overproduction of this class of lipoproteins.

The diagnosis should include the presence of at least one first-degree relative with hypertriglycerideremia. FHTG should be distinguished from FCHL and FDBL, as the latter require more vigorous treatment to prevent coronary or peripheral vascular disease. The differentiation is usually possible on clinical grounds, in that lower LDL cholesterol levels accompany FHTG, but measurement of normal apoB levels in FHTG may be helpful in ambiguous situations.

A more severe hypertriglycerideremia characterized by increased levels of chylomicrons as well as VLDL particles (Frederickson type V) may occasionally be encountered. Triglyceride levels are often >1,000 mg/dL. The disease is rarely seen in children. In contrast to chylomicronemia (Frederickson type I), LPL or apoC-II deficiency is not present. These patients often develop eruptive xanthomas in adulthood, whereas type IV hypertriglycerideremia individuals do not. Acute pancreatitis may be the presenting illness. As with other hypertriglycerideremias, excessive alcohol consumption and estrogen therapy can exacerbate the disease.

Secondary causes of transient hypertriglycerideremia should be ruled out before making a diagnosis of FHTG. A diet high in simple sugars and carbohydrates, or excessive alcohol consumption as well as estrogen therapy may exacerbate hypertriglycerideremia. Adolescents and adults should be questioned about excessive consumption of soda and other sweetened drinks, as it is common to encounter people who drink supersized drinks or multiple 12 oz cans of sweetened drinks daily. Cessation of this practice often results in dramatic fall in triglyceride levels as well as weight among those who are obese. HDL cholesterol levels will tend to rise as BMI stabilizes.

Pediatric diseases associated with hyperlipidemia include hypothyroidism, nephrotic syndrome, biliary atresia, glycogen storage disease, Niemann-Pick disease, Tay-Sachs disease, systemic lupus erythematosus, hepatitis, and anorexia nervosa (Table 86-9). Certain medications exacerbate hyperlipidemia, including isoretinoin (Accutane), thiazide diuretics, oral contraceptives, steroids, β blockers, immunosuppressants, and protease inhibitors used in the treatment of HIV.

Treatment of hypertriglycerideremia in children rarely requires medication unless levels >1,000 mg/dL persist after dietary restriction of fats, sugars, and carbohydrates, accompanied by increased physical activity. In such cases, the aim is to prevent episodes of pancreatitis. The common use of fibrates (fenofibric acid) and niacin in adults with hypertriglycerideremia is not recommended in children. HMG-CoA reductase inhibitors are reasonably effective in lowering triglyceride levels, and there is considerably more experience documenting the safety and efficacy of this class of lipid-lowering medications in children. In adults, prescription (Lovaza, Vascepa) and nonprescription fish oils have been approved by the FDA as adjuncts to diet in the treatment of severe hypertriglycerideremias.

Figure 86-13 Milky plasma from patient with acute abdominal pain. (From Durrington P: Dyslipidaemia, Lancet 362:717–731, 2003.)
Table 86-9  Secondary Causes of Hyperlipidemia

<table>
<thead>
<tr>
<th>HYPERCHOLESTEROLEMIA</th>
<th>Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causative factor</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Drugs</td>
<td>Progestrone, thiazides, Metformin, cyclosporine</td>
</tr>
</tbody>
</table>

HYPERTRIGLYCERIDEMIA

<table>
<thead>
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<th>Hypertriglyceridemia</th>
<th>Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causes</td>
<td>Obesity, alcohol, malnutrition</td>
</tr>
<tr>
<td>Drugs</td>
<td>Estrogen, thiazides</td>
</tr>
</tbody>
</table>

REduced HIGH-DENSITY LIPOPROTEIN

<table>
<thead>
<tr>
<th>Reducing HDL cholesterol</th>
<th>Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td>β blockers, anabolic steroids</td>
</tr>
</tbody>
</table>

Hepatic Lipase Deficiency

Hepatic lipase deficiency is a very rare autosomal recessive condition causing elevation in both plasma cholesterol and triglycerides. Hepatic lipase hydrolyzes triglycerides and phospholipids in VLDL remnants and LDL, preventing their conversion to LDL. HDL cholesterol levels tend to be increased rather than decreased, suggesting the diagnosis. Laboratory confirmation is established by measuring hepatic lipase activity in heparinized plasma.

Disorders of High-Density Lipoprotein Metabolism

Primary Hypoalphalipoproteinemia

Isolated low HDL cholesterol is a familial condition that often follows a pattern suggestive of autosomal dominant inheritance but may occur independent of family history. It is the most common disorder of HDL metabolism. It is defined as HDL cholesterol <10th percentile for gender and age with normal plasma triglycerides and LDL cholesterol. Whether it is associated with more rapid atherosclerosis is uncertain. It appears to be related to a reduction in apoA-I synthesis and increased catabolism of HDL. Secondary causes of low HDL cholesterol, such as the metabolic syndrome, and rare diseases such as LCAT deficiency and Tangier disease must be ruled out.

Familial Hypoalphalipoproteinemia

This is an unusual condition conferring decreased risk for CHD among family members. Plasma levels of HDL cholesterol exceed 80 mg/dL.

Familial Apolipoprotein A-I Deficiency

Mutations in the apoA-I gene may result in complete absence of plasma HDL. Nascent HDL is produced in the liver and small intestine. Free cholesterol from peripheral cells is esterified by LCAT, enabling formation of mature HDL particles. ApoA-I is required for normal enzymatic function of LCAT. The resultant accumulation of free cholesterol in the circulation eventually leads to corneal opacities, planar xanthomas, and premature atherosclerosis. Some patients, however, may have mutations of apoA-I that result in very rapid catabolism of the protein not associated with atherogenesis, despite HDL cholesterol levels in the 15-30 mg/dL range.

Tangier Disease

This is an autosomal codominant disease associated with levels of HDL cholesterol <5 mg/dL. It is caused by mutations in ABCA1, a protein that facilitates the binding of cellular cholesterol to apoA-I. This results in free cholesterol accumulation in the reticuloendothelial system manifested by tonsillar hypertrophy of a distinctive orange color and hepatosplenomegaly. Intermittent peripheral neuropathy may occur from cholesterol accumulation in Schwann cells. Diagnosis should be suspected in children with enlarged orange tonsils and extremely low HDL cholesterol levels.

Familial Lecithin–Cholesterol Acyltransferase Deficiency

Mutations affecting LCAT interfere with the esterification of cholesterol, thereby preventing formation of mature HDL particles. This is associated with rapid catabolism of apoA-I. Free circulating cholesterol in the plasma is greatly increased, which leads to corneal opacities and HDL cholesterol levels <10 mg/dL. Partial LCAT deficiency is known as “fish-eye” disease. Complete deficiency causes hemolytic anemia and progressive renal insufficiency early in adulthood. This rare disease is not thought to cause premature atherosclerosis. Laboratory confirmation is based on demonstration of decreased cholesterol esterification in the plasma.

Cholesteryl Ester Transfer Protein Deficiency

Mutations involving the CETP gene are localized to chromosome 16q21. CETP facilitates the transfer of lipoproteins from mature HDL to and from VLDL and chylomicron particles, thus ultimately regulating the rate of cholesterol transport to the liver for excretion in the bile. About half of mature HDL-2 particles are directly removed from the circulation by HDL receptors on the surface of the liver. The other half of cholesteryl esters in the core of HDL exchange with triglycerides in the core of apoB lipoproteins (VLDL, IDL, LDL) for transport to the liver. Homozygous deficiency of CETP has been observed in subsets of the Japanese population with extremely high HDL cholesterol levels (>150 mg/dL).

Conditions Associated with Low Cholesterol

Disorders of apoB-containing lipoproteins and intracellular cholesterol metabolism are associated with low plasma cholesterol.

Abetalipoproteinemia

This rare autosomal recessive disease is caused by mutations in the gene encoding microsomal triglyceride transfer protein necessary for the transfer of lipids to nascent chylomicrons in the small intestine and VLDL in the liver. This results in absence of chylomicrons, VLDL, LDL, and apoB, and very low levels of plasma cholesterol and triglycerides. Fat malabsorption, diarrhea, and failure to thrive present in early childhood. Spino-cerebellar degeneration, secondary to vitamin E deficiency, manifests in loss of deep tendon reflexes progressing to ataxia and lower extremity spasticity by adulthood. Patients with abetalipoproteinemia also acquire a progressive pigmentary retinopathy associated with decreased night and color vision and eventual blindness. The neurologic symptoms and retinopathy may be mistaken for Friedreich ataxia. Differentiation from Friedreich ataxia is suggested by the presence of malabsorption and acanthocytosis on peripheral blood smear in abetalipoproteinemia. Many of the clinical manifestations of the disease are a result of malabsorption of fat-soluble vitamins, such as vitamins A, D, E, and K. Early treatment with supplemental vitamins, especially E, may significantly slow the development of neurologic sequelae. Vitamin E is normally transported from the small intestine to the liver by chylomicrons, where it is dependent on the endogenous VLDL pathway for delivery into the circulation and peripheral tissues. Parents of children with abetalipoproteinemia have normal blood lipid and apoB levels.

Familial Hypobetalipoproteinemia

Familial homozygous hypobetalipoproteinemia is associated with symptoms very similar to those of abetalipoproteinemia, but the inheritance pattern is autosomal codominant. The disease is caused by mutations in the gene encoding apoB-100 synthesis. It is distinguishable from abetalipoproteinemia in that heterozygous parents of probands
have plasma LDL cholesterol and apoB levels less than half normal. There are no symptoms or sequelae associated with the heterozygous condition.

The selective inability to secrete apoB-48 from the small intestine results in a condition resembling abetalipoproteinemia or homozygous hypobetalipoproteinemia. Sometimes referred to as Anderson disease, the failure of chylomicron absorption causes steatorrhea and fat-soluble vitamin deficiency. The blood level of apoB-100, derived from normal hepatocyte secretion, is normal in this condition.

**Smith-Lemli-Opitz Syndrome**

Patients with Smith-Lemli-Opitz syndrome (SLOS) often have multiple congenital anomalies and developmental delay caused by low plasma cholesterol and accumulated precursors (Tables 86-10 and 86-11). Family pedigree analysis has revealed its autosomal recessive inheritance pattern. Mutations in the DHCR7 (7-dehydrocholesterol-Δ7 reductase) gene result in deficiency of the microsomal enzyme DHCR7, which is necessary to complete the final step in cholesterol synthesis. It is not known why defects in cholesterol synthesis result in congenital malformations, but as cholesterol is a major component of myelin and a contributor to signal transduction in the developing nervous system, neurodevelopment is severely impaired. The incidence of SLOS is estimated to be 1 in 20,000–60,000 births among whites, with a somewhat higher frequency in Hispanics and lower incidence in individuals of African descent.

Spontaneous abortion of SLOS fetuses may occur. Type II SLOS often leads to death by the end of the neonatal period. Survival is unlikely when the plasma cholesterol level is <20 mg/dL. Laboratory measurement should be performed by gas chromatography, as standard techniques for lipoprotein assay include measurement of cholesterol precursors, which may yield a false-positive result. Milder cases may not present until late childhood. Phenotypic variance ranges from microcephaly, cardiac and brain malformation, and multisystem failure to only subtle dysmorphic features and mild developmental delay. Treatment includes supplemental dietary cholesterol (egg yolk) and HMG-CoA reductase inhibition to prevent the synthesis of toxic precursors proximal to the enzymatic block.

**Disorders of Intracellular Cholesterol Metabolism**

**Cerebrotendinous Xanthomatosis**

This autosomal recessive disorder presents clinically in late adolescence with tendon xanthomas, cataracts, and progressive neurodegeneration. It is caused by tissue accumulation of bile acid intermediates shunted into cholestanol resulting from mutations in the gene for sterol 27-hydroxylase. This enzyme is necessary for normal mitochondrial synthesis of bile acids in the liver. Early treatment with chenodeoxycholic acid reduces cholesterol levels and prevents the development of symptoms.

**Wolman Disease and Cholesterol Ester Storage Disease**

These autosomal recessive disorders are caused by lack of lysosomal acid lipase. After LDL cholesterol is incorporated into the cell by endocytosis, it is delivered to lysosomes where it is hydrolyzed by lysosomal lipase. Failure of hydrolysis because of complete absence of the enzyme causes accumulation of cholesteryl esters within the cells. Hepatosplenomegaly, steatorrhea, and failure to thrive occur during early infancy, leading to death by the age of 1 yr. In cholesterol ester storage disease, a less-severe form than Wolman disease, there is low but detectable acid lipase activity.

**Niemann-Pick Disease Type C**

This is a disorder of intracellular cholesterol transport characterized by accumulation of cholesterol and sphingomyelin in the central nervous and reticuloendothelial systems. Death from this autosomal recessive neurologic disease usually occurs by adolescence.

**Lipoprotein Patterns in Children and Adolescents**

Table 86-12, derived primarily from the Lipid Research Clinics Population Studies, shows the distribution of lipoprotein levels in American
Table 86-12  Plasma Cholesterol and Triglyceride Levels in Childhood and Adolescence: Means and Percentiles

<table>
<thead>
<tr>
<th></th>
<th>Total Triglyceride (mg/dL)</th>
<th>Total Cholesterol (mg/dL)</th>
<th>Low-Density Lipoprotein Cholesterol (mg/dL)</th>
<th>High-Density Lipoprotein Cholesterol (mg/dL)*</th>
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<tbody>
<tr>
<td></td>
<td>5TH</td>
<td>MEAN</td>
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<td>90TH</td>
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<tr>
<td>Cord</td>
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<td>—</td>
</tr>
<tr>
<td>1-4 YR</td>
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</tr>
<tr>
<td>Male</td>
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<td>56</td>
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<td>34</td>
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<tr>
<td>5-9 YR</td>
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<td>10-14 YR</td>
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<tr>
<td>Female</td>
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<td>72</td>
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<tr>
<td>15-19 YR</td>
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<td>88</td>
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<tr>
<td>Female</td>
<td>36</td>
<td>73</td>
<td>85</td>
<td>112</td>
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</tbody>
</table>

*Note that different percentiles are listed for HDL cholesterol.

young at various ages. Total plasma cholesterol rises rapidly from a mean of 68 mg/dL at birth to a level approximately twice that by the end of the neonatal period. A very gradual rise in total cholesterol level occurs until puberty, at which time the mean level reaches 160 mg/dL. Total cholesterol falls transiently during puberty, in males because of a small decrease in HDL cholesterol, and in females secondary to a slight fall in LDL cholesterol. Blood cholesterol levels track reasonably well as individuals age.

High blood cholesterol tends to aggregate in families, a reflection of genetic and environmental influences. Acceptable total cholesterol among children and adolescents is <170 mg/dL; borderline is 170-199 mg/dL; and high >200 mg/dL. Acceptable LDL cholesterol is <110 mg/dL; borderline 110-129 mg/dL; and high >130 mg/dL. HDL cholesterol should be >40 mg/dL.

**Blood Cholesterol Screening**

Previous guidelines for cholesterol measurement in children utilized a targeted approach. This meant obtaining a fasting lipid panel in a select group of children between the ages of 2 and 10 yr who met at least 1 of the following criteria:

- Parents or grandparents have documented premature coronary artery disease (before the age of 55 yr if male and 65 yr if female)
- Parents have been found to have high blood concentration of cholesterol (>240 mg/dL)
- Family history is unobtainable, particularly those with other risk factors such as obesity, hypertension, smoking, and/or diabetes mellitus

Reliance on family history of premature heart disease or known parental heart disease, or known parental hypercholesterolemia was considered by some to be too insensitive and difficult to apply. Data from a large cohort of 5th grade school children who had comprehensive screening of CVD risk factors conducted by the Coronary Artery Risk Detection in Appalachian Communities (CARDIAC) Project, which utilized a universal screening approach, found 36% of children with severe dyslipidemia did not fulfill criteria for the selective screening approach.

The American Academy of Pediatrics began recommending a universal screening approach for cholesterol screening to all children in 2011. They recommend a lipid profile to be checked for all children between the ages of 2 and 10 yr who met at least 1

### Risk Assessment and Treatment of Hyperlipidemia

The NCEP recommends a population-based approach toward healthy lifestyle applicable to all children, and an individualized approach directed at those children at high risk (Fig. 86-14). The important focus is on maintenance of a healthy lifestyle rather than aggressive weight reduction is recommended by the American Academy of Pediatrics.

All children with dyslipidemias are stratified according to the presence of "high-level" or "moderate-level" risk factors to determine their ultimate treatment. High-level risk factors are defined as the following: hypertension requiring drug therapy (blood pressure ≥99th percentile + 5 mm Hg), current cigarette smoker, BMI at the ≥97th percentile, presence of type I or type II diabetes mellitus, chronic kidney disease, postorthoplastic heart transplant, and/or Kawasaki disease with current aneurysms. Moderate-level risk factors are defined as the following: hypertension that does not require drug therapy, BMI at the ≥95th percentile but <97th percentile, HDL cholesterol <40 mg/dL, Kawasaki disease with regressed coronary aneurysms, chronic inflammatory disease, HIV infection, and/or presence of nephrotic syndrome.

The Children’s Heart Health Integrated Lifestyle Diet-1 (CHILD-1) diet is the first level of dietary change to be recommended for all children with dyslipidemias. The CHILD-1 diet is specially designed for children with risk factors for coronary artery disease and focuses on such things as limitation of dietary cholesterol to no more than 300 mg/ day, limitation of sugary drink consumption, use of reduced fat/skim milk, avoiding foods high in trans-type fats, limitation of foods high in sodium, and encouraging consumption of foods high in fiber. Specific recommendations are dependent on the child’s age.

The use of the Cardiovascular Health Integrated Lifestyle Diet-2 (CHILD-2) diet is recommended if the CHILD-1 diet alone is unsuccessful. Although similar in many aspects to the CHILD-1 diet, the CHILD-2 diet is geared toward a specific dyslipidemia type, where the CHILD-2 LDL diet is recommended for those children with elevated LDL levels and the CHILD-2 TG diet is recommended for those children presenting with elevated triglycerides. The basic recommendations of calorie consumption for the CHILD-2 diet are as follows: 25% to 30% of calories from fat, less than or equal to 7% of calories from saturated fat about 10% of calories from monounsaturated fat, less than 200 mg/d of cholesterol. If the CHILD-2 LDL diet is recommended, the use of plant sterols and water-soluble fiber is emphasized. If the CHILD-2 TG diet is recommended, the increasing consumption of complex carbohydrates and omega-3 fatty acids is emphasized.

If followed, these dietary recommendations will provide adequate calories for optimal growth and development without promoting obesity. Compliance on the part of children and their caregivers is challenging in today's society. Children learn eating habits from their parents. Successful adoption of a healthier lifestyle is far more likely to occur if meals and snacks in the home are applicable to the entire family rather than an individual child. A regular time for meals together as a family is desirable. Grandparents and other nonparental caregivers sometimes need to be reminded not to indulge the child who is on a restricted diet. Additionally, the rise in obesity is prompting some school districts to restrict sweetened drink availability, and offer more nutritious cafeteria selections.

As mentioned, changes in physical activity habits are also an important part of the initial lifestyle modification. The National Association for Sport and Physical Education recommends that children should accumulate at least 60 minutes of age-appropriate physical activity on most days of the week. Extended periods (2 hr or more) of daytime inactivity are discouraged, as is more than 2 hr of television and other forms of screen time. Unfortunately, the continued rise in sedentary activity among our youth contributes to the increase in obesity nationwide, which in turn, leads to the increasing prevalence of other risk factors such as hypertension.

**Pharmacologic Therapy.** See Tables 86-13 and 86-14. The use of pharmacotherapy to treat dyslipidemias in children has been advocated by the American Academy of Pediatrics since the
Figure 86-14 Algorithm of the evaluation, risk assessment, follow-up, and treatment of children based on low-density lipoprotein (LDL) cholesterol levels. FLP, fasting lipid profile; TG, triglycerides. (From Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary report. Pediatrics 128(Suppl 5):S213–S256, 2011, Fig. 9-1.)

Table 86-13 Drugs Used for the Treatment of Hyperlipidemia

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MECHANISM OF ACTION</th>
<th>INDICATION</th>
<th>STARTING DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMG-CoA reductase inhibitors (statins)</td>
<td>↓ Cholesterol and VLDL synthesis</td>
<td>Elevated LDL</td>
<td>5-80 mg qhs</td>
</tr>
<tr>
<td></td>
<td>↑ Hepatic LDL receptors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bile acid sequestrants:</td>
<td>↑ Bile and excretion</td>
<td>Elevated LDL</td>
<td>4-32 g daily</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td></td>
<td></td>
<td>5-40 g daily</td>
</tr>
<tr>
<td>Colestipol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>↓ Hepatic VLDL synthesis</td>
<td>Elevated LDL</td>
<td>100-2,000 mg tid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Elevated LDL</td>
<td></td>
</tr>
<tr>
<td>Fibric acid derivatives:</td>
<td>↑ LPL</td>
<td>Elevated TG</td>
<td>600 mg bid</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>↓ VL LDL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fish oils</td>
<td>↓ VL LDL</td>
<td>Elevated TG</td>
<td>3-10 g daily</td>
</tr>
<tr>
<td>Cholesterol absorption inhibitors:</td>
<td>↓ Intestinal absorption cholesterol</td>
<td>Elevated LDL</td>
<td>10 mg daily</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LDL, low-density lipoprotein; LPL, lipoprotein lipase; TG, triglyceride; VLDL, very-low-density lipoprotein.
Side Effects of Lipid-Lowering Drugs

<table>
<thead>
<tr>
<th>DRUG AND SITE OR TYPE OF EFFECT</th>
<th>EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STATINS</strong></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>Rash</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Loss of concentration, sleep disturbance, headache, peripheral neuropathy</td>
</tr>
<tr>
<td>Liver</td>
<td>Hepatitis, loss of appetite, weight loss, and increases in serum aminotransferases to 2-3 times the upper limit of the normal range</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Abdominal pain, nausea, diarrhea</td>
</tr>
<tr>
<td>Muscles</td>
<td>Muscle pain or weakness, myositis (usually with serum creatine kinase &gt;1,000U/L), rhabdomyolysis with renal failure</td>
</tr>
<tr>
<td>Immune system</td>
<td>Lupus-like syndrome (lovastatin, simvastatin, or fluvastatin)</td>
</tr>
<tr>
<td>Protein binding</td>
<td>Diminished binding of warfarin (lovastatin, simvastatin, fluvastatin)</td>
</tr>
<tr>
<td><strong>BILE ACID-BINDING RESINS</strong></td>
<td>Abdominal fullness, nausea, gas, constipation, hemorrhoids, anal fissure, activation of diverticulitis, diminished absorption of vitamin D in children</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Mild serum aminotransferase elevations, which can be exacerbated by concomitant treatment with a statin</td>
</tr>
<tr>
<td>Liver</td>
<td>Increases in serum triglycerides of ≈10% (greater increases in patients with hypertriglyceridemia)</td>
</tr>
<tr>
<td>Metabolic system</td>
<td>Hypercholesteremic acidosis in children and patients with renal failure (cholestyramine)</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>Binding of warfarin, digoxin, thiazide diuretics, thyroxine, statins</td>
</tr>
<tr>
<td>Drug interactions</td>
<td></td>
</tr>
<tr>
<td><strong>NICOTINIC ACID</strong></td>
<td>Flushing, dry skin, pruritus, ichthyosis, acanthosis nigricans</td>
</tr>
<tr>
<td>Skin</td>
<td>Nasal stuffiness</td>
</tr>
<tr>
<td>Eyes</td>
<td>Conjunctivitis, cystoid macular edema, retinal detachment</td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>Supraventricular arrhythmias</td>
</tr>
<tr>
<td>Heart</td>
<td>Heartburn, loose bowel movements or diarrhea</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Mild increase in serum aminotransferases, hepatitis with nausea and fatigue</td>
</tr>
<tr>
<td>Liver</td>
<td>Myositis</td>
</tr>
<tr>
<td>Muscles</td>
<td>Hyperglycemia (incidence: ≈5% higher in patients with diabetes), increase of 10% in serum uric acid</td>
</tr>
<tr>
<td>Metabolic system</td>
<td></td>
</tr>
<tr>
<td><strong>FIBRATES</strong></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>Rash</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Stomach upset, abdominal pain (mainly gemfibrozil), cholesterol-saturated bile, increase of 1-2% in gallstone incidence</td>
</tr>
<tr>
<td>Genitourinary tract</td>
<td>Erectile dysfunction (mainly clofibrate)</td>
</tr>
<tr>
<td>Muscles</td>
<td>Myositis with impaired renal function</td>
</tr>
<tr>
<td>Plasma proteins</td>
<td>Interference with binding of warfarin, requiring reduction in the dose of warfarin by ≈30%</td>
</tr>
<tr>
<td>Liver</td>
<td>Increased serum aminotransferases</td>
</tr>
</tbody>
</table>


Inception of screening and treatment guidelines from the NCEP in 1992. Although the treatment guidelines have been slightly modified by the American Academy of Pediatrics since that time, pharmacologic therapy with cholesterol-lowering medication still remains a cornerstone of therapy for children who fail to respond to a 6 mo period of rigorous lifestyle modification. Drug therapy should be considered when one of the following conditions are met, which are also shown in Figure 86-14:

- LDL cholesterol remains >190 mg/dL
- LDL cholesterol remains >160 mg/dL, with presence of 1 high-level risk factor and/or at least 2 moderate-level risk factors
- LDL cholesterol remains >130 mg/dL, with presence of at least 2 high-level risk factors, 1 high-level risk factor, and at least 2 moderate-level risk factors, or evidence of coronary artery disease

Considerable experience with drug therapy in children and adolescents with hyperlipidemia over the past 20 yr has expanded therapeutic options, improved compliance, and enhanced efficacy. In the past, the mainstay of drug therapy was bile acid sequestrants such as cholestyramine and colestipol because they were not systemically absorbed. Interruption of the enterohepatic circulation of bile acids promotes synthesis in the liver of new bile acids from cholesterol. Gastrointestinal side effects and taste resulted in less than desirable compliance, even when there were few viable options.

**HMG-CoA reductase inhibitors**, also known as "statins" are remarkably effective in lowering LDL cholesterol levels and reducing plaque inflammation, thereby reducing the likelihood of a sudden coronary event in an at-risk adult within weeks of starting the medication. As a class, they work by blocking the intrahepatic biosynthesis of cholesterol, thereby stimulating the production of more LDL receptors on the cell surface and facilitating the uptake of LDL cholesterol from the bloodstream. The NCEP Adult Treatment Panel advocates aggressive lowering of LDL to below 70 mg/dL in individuals with known coronary artery disease. This information is relevant because a child who fulfills criteria for consideration of cholesterol-lowering medication will almost always have inherited the condition from one of the child’s parents. Not infrequently, when providing care for the child, questions come up about screening and treatment of parents or grandparents. Statins are equally effective in children, capable of lowering LDL-C levels by 50% when necessary. They are considered first-line therapy for children who meet criteria for pharmacologic therapy. They also will effect a modest reduction in triglycerides and an inconsistent increase in HDL cholesterol. Their side-effect profile, mainly liver dysfunction and rarely rhabdomyolysis with secondary renal failure, should be taken into consideration before prescribing the drug. However, there has been no evidence to date that complications are any more frequent in children than adults, and skeletal muscle discomfort seems to be somewhat less of a problem. Drug interactions may occur as well, so careful attention should be paid to a child’s active prescriptions to avoid potentiation of the aforementioned side effects. Children should have liver enzymes monitored regularly, and creatine phosphokinase measured if muscle aches or weakness occurs. Liver enzymes may be allowed to rise 3-fold before discontinuing the drug. There is a suggested link between the use of statins and increased risk of developing type II diabetes mellitus in
adults, but these results have not been replicated in children. It should be reemphasized that children with modest elevations in cholesterol, such as that seen in polygenic hypercholesterolemia, are not, as a rule, candidates for statins because of their side-effect profile. Statins should be started at the lowest effective dose and allowed at least 8 wk to achieve their peak effect. If LDL levels are not at goal, which in children who are treated is generally established to be <130 mg, then the medication may be titrated upwards with careful monitoring of side effects.

Other cholesterol-lowering medications such as nicotinic acid and fibrate have been used far less often in children than bile acid sequestrants and statins. Nicotinic acid and fibrates have been used selectively in children with marked hypertriglyceridemia (>500 mg/dL) at risk for acute pancreatitis, though dietary restriction of complex sugars and carbohydrates will usually result in significant lowering of triglyceride levels. Current guidelines recommend treatment of LDL cholesterol as the initial priority and after LDL levels are at goal, then if triglycerides remain between 200 and 499 mg/dL and non-HDL cholesterol remains ≥145 mg/dL, treatment, pharmacologic treatment to reduce triglyceride levels is indicated. Omega-3 fatty acid supplementation, available both over the counter and in prescription form, is a safe and useful treatment approach to reduce triglyceride levels by decreasing the hepatic synthesis of triglycerides.

Ezetimibe has proven to be useful in the pediatric population because of its efficacy and low side-effect profile. Ezetimibe reduces plasma LDL cholesterol by blocking sterol absorption in enterocytes. The drug is marketed as an adjunct to statins when adult subjects are not achieving sufficient blood lipid lowering with statins alone. Not surprisingly, large clinical trials of ezetimibe used as monotherapy in children have not been conducted because the potential market in the pediatric age group is small. Nevertheless, there are sufficient reports in the literature documenting the effectiveness of this medication without worrisome side effects that one can feel on relatively safe grounds recommending it instead of a statin when moderate hypercholesterolemia is encountered, or apprehension from parents makes using a statin difficult.

Bibliography is available at Expert Consult.

86.4 Lipidoses (Lysosomal Storage Disorders)
Margaret M. McGovern and Robert J. Desnick

The lysosomal lipid storage diseases are diverse disorders, each caused by an inherited deficiency of a specific lysosomal hydrolase leading to the intralysosomal accumulation of the enzyme’s particular substrate (Table 86-15 and 86-16). With the exception of Wolman disease and cholesterol ester storage disease, the lipid substrates share a common structure that includes a ceramide backbone (2-N-acylsphingosine) from which the various sphingolipids are derived by substitution of hexoses, phosphorylcholine, or 1 or more sialic acid residues on the terminal hydroxyl group of the ceramide molecule. The pathway of sphingolipid metabolism in nervous tissue (Fig. 86-15) and in visceral organs (Fig. 86-16) is known; each catabolic step, with the exception of the catabolism of lactosylceramide, has a genetically determined metabolic defect and a resultant disease. Because sphingolipids are essential components of all cell membranes, the inability to degrade these substances and their subsequent accumulation results in the physiologic and morphologic alterations and characteristic clinical manifestations of the lipid storage disorders (see Table 86-15). Progressive lysosomal accumulation of glycosphingolipids in the central nervous system leads to neurodegeneration, whereas storage in visceral cells can lead to organomegaly, skeletal abnormalities, pulmonary infiltration, and other manifestations. The storage of a substrate in a specific tissue is dependent on its normal distribution in the body.

Diagnostic assays for the identification of affected individuals rely on the measurement of the specific enzymatic activity in isolated leukocytes or cultured fibroblasts or lymphoblasts. Figure 86-17 shows an approach to differentiating these disorders. For most disorders, carrier identification and prenatal diagnosis are available; a specific diagnosis is essential to permit genetic counseling. Neonatal screening using dried blood spots and performing enzyme assays and mutational analysis for Gaucher, Pompe, Fabry, and Niemann-Pick diseases are undergoing pilot studies. The characterization of the genes that encode the specific enzymes required for sphingolipid metabolism permit the development of therapeutic options, such as recombinant enzyme replacement therapy, as well as the potential of cell or gene therapy. Identification of specific disease-causing mutations improves diagnosis, prenatal detection, and carrier identification. For several disorders (Gaucher, Fabry, and Niemann-Pick types A and B disease), it has been possible to make genotype–phenotype correlations that predict disease severity and allow more precise genetic counseling. Inheritance is autosomal recessive except for X-linked Fabry disease.

GM1, GANGLIOSIDOSIS

GM1 gangliosidosis most frequently presents in early infancy, but has been described in patients with juvenile and adult onset subtypes. Inherited as an autosomal recessive trait, each subtype results from a different gene mutation that leads to the deficient activity of β-galactosidase, a lysosomal enzyme encoded by a gene on chromosome 3 (3p21.33). Although the disorder is characterized by the pathologic accumulation of GM1 gangliosides in the lysosomes of both neural and visceral cells, GM1 ganglioside accumulation is most marked in the brain. In addition, keratan sulfate, a mucopolysaccharide, accumulates in liver and is excreted in the urine of patients with GM1 gangliosidosis. The β-galactosidase gene has been isolated and sequenced; mutations causing the disease subtypes have been identified.

The clinical manifestations of the infantile form of GM1 gangliosidosis may be evident in the newborn as hepatosplenomegaly, edema, and skin eruptions (angiokeratoma). It most frequently presents in the first 6 mo of life with developmental delay followed by progressive psychomotor retardation and the onset of tonic–clonic seizures. A typical facies is characterized by low-set ears, frontal bossing, a depressed nasal bridge, and an abnormally long philtrum. Up to 50% of patients have a macular cherry-red spot. Hepatosplenomegaly and skeletal abnormalities similar to those of the mucopolysaccharidoses, including anterior beaking of the vertebrae, enlargement of the sella turcica, and thickening of the calvarium, are present. By the end of the first year of life, most patients are blind and deaf, with severe neurologic impairment characterized by cerebellar rigidity. Death usually occurs by 3–4 yr of age. The juvenile-onset form of GM1 gangliosidosis is clinically distinct, with a variable age at onset. Affected patients present primarily with neuropsychiatric symptoms including ataxia, dystonia, intellectual disability, and spasticity. Deterioration is slow; patients may survive through the 4th decade of life. These patients lack the visceral involvement, facial abnormalities, and skeletal features seen in type 1 disease. Adult-onset patients have been described who present with gait and speech abnormalities, dystonia and mild skeletal abnormalities. There is no specific treatment for either form of GM1 gangliosidosis.

The diagnosis of GM1 gangliosidosis should be suspected in infants with typical clinical features and is confirmed by the demonstration of the deficiency of β-galactosidase activity in peripheral leukocytes. Other disorders that share some of the features of the GM1 gangliosidoses include Hurler disease (mucopolysaccharidosis type I), I-cell disease, and Niemann-Pick disease (NPD) type A, which can each be distinguished by the demonstration of their specific enzymatic deficiencies. Carriers of the disorder are detected by the measurement of the enzymatic activity in peripheral leukocytes or by identifying the specific gene mutations; prenatal diagnosis is accomplished by determination of the enzymatic activity in cultured amniocytes or chorionic villi or identification of the specific disease-causing mutations. Currently only supportive therapy is available for patients with GM1 gangliosidosis. However, studies in mice with GM1-gangliosidosis have demonstrated that orally administered N-octyl-4-epi-β-valienamine
Table 86-15  Clinical Findings in Lysosomal Storage Diseases

<table>
<thead>
<tr>
<th>NOMENCLATURE</th>
<th>ENZYME DEFECT</th>
<th>HYDROPS FETALIS</th>
<th>COARSE FACIAL FEATURES</th>
<th>DYSTOSIS MULTIPLEX</th>
<th>HEPATOSPLENOMEGALY</th>
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<td>β-Hexosaminidases A and B</td>
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<tr>
<td>Wolman disease</td>
<td>Acid lipase</td>
<td>(+)</td>
<td>–</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Ceroid lipofuscinosis, infantile (Santavuori-Haltia)</td>
<td>Palmitoyl-protein thioesterase (CLN1)</td>
<td>–</td>
<td>–</td>
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<td></td>
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<tr>
<td>Ceroid lipofuscinosis, late infantile (Jansky-Bielschowsky)</td>
<td>Pepstatin-insensitive peptidase (CLN2); variants in Finland (CLN5), Turkey (CLN7), and Italy (CLN6)</td>
<td>–</td>
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<tr>
<td>Ceroid lipofuscinosis, juvenile (Spielmeyer-Vogt)</td>
<td>CLN3, membrane protein</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Ceroid lipofuscinosis, adult (Kufs, Parry)</td>
<td>CLN4, probably heterogeneous</td>
<td>(+)</td>
<td>–</td>
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<tr>
<td>Oligosaccharidoses</td>
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<tr>
<td>Aspartylglucosaminuria</td>
<td>Aspartylglucosylaminase</td>
<td>–</td>
<td>+</td>
<td>(+)</td>
<td></td>
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<tr>
<td>Fucosidosis</td>
<td>α-Fucosidase</td>
<td>–</td>
<td>++</td>
<td>(+)</td>
<td></td>
</tr>
<tr>
<td>α-Mannosidosis</td>
<td>α-Mannosidase</td>
<td>–</td>
<td>++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>β-Mannosidosis</td>
<td>β-Mannosidase</td>
<td>–</td>
<td>+</td>
<td>(+)</td>
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<tr>
<td>Schindler disease</td>
<td>α-N-Acetylgalactosaminidase</td>
<td>–</td>
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<tr>
<td>Sialidosis I</td>
<td>Sialidase</td>
<td>(+)</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Sialidosis II</td>
<td>Sialidase</td>
<td>(+)</td>
<td>++</td>
<td>+</td>
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</tbody>
</table>

++, Prominent; +, often present; (+), inconstant or occurring later in the disease course; –, not present; GAG, glycosaminoglycans. Modified from Hoffmann GF, Nyhan WL, Zschoke J, et al: Storage disorders in inherited metabolic diseases, Philadelphia, 2002, Lippincott Williams & Wilkins, pp. 346–351.

(ENOEV), which stabilizes the mutant enzyme protein produced by affected animals, crossed the brain and improved neurologic deterioration suggesting that this approach may be useful to study in humans.

THE GM2 GANGLIOSIDOSES
The GM2 gangliosidoses include Tay-Sachs disease and Sandhoff disease; each results from the deficiency of β-hexosaminidase activity and the lysosomal accumulation of GM2 gangliosides, particularly in the central nervous system. Both disorders have been classified into infantile-, juvenile-, and adult-onset forms based on the age at onset and clinical features. β-Hexosaminidase occurs as 2 isoforms: β-hexosaminidase A, which is composed of 1 α and 1 β subunit, and β-hexosaminidase B, which has 2 β subunits. β-Hexosaminidase A deficiency results from mutations in the α subunit and causes Tay-Sachs disease, whereas mutations in the β-subunit gene result in the deficiency of both β-hexosaminidases A and B and cause Sandhoff disease.
### Table 86-15

<table>
<thead>
<tr>
<th>CARDIAC INVOLVEMENT</th>
<th>MENTAL DETERIORATION</th>
<th>MYOCLONUS</th>
<th>SPASTICITY</th>
<th>PERIPHERAL NEUROPATHY</th>
<th>CHERRY-RED SPOT</th>
<th>CORNEAL CLOUDING</th>
<th>ANGIokeratomaTATA</th>
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<tbody>
<tr>
<td>++</td>
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<td>(+)</td>
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More than 50 mutations have been identified; most are associated with the infantile forms of disease. Three mutations account for >98% of mutant alleles among Ashkenazi Jewish carriers of Tay-Sachs disease, including 1 allele associated with the adult-onset form. Mutations that cause the subacute or adult-onset forms result in enzyme proteins with residual enzymatic activities, the levels of which correlate with the severity of the disease.

Patients with the infantile form of Tay-Sachs disease have clinical manifestations in infancy including loss of motor skills, increased startle reaction, and macular pallor and retinal cherry-red spots (see Table 86-15). Affected infants usually develop normally until 4-5 mo of age when decreased eye contact and an exaggerated startle response to noise (hyperacusis) are noted. Macrocephaly, not associated with...
Table 86-16  Symptoms Encountered in Patients with Lysosomal Storage Disorders

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>MANIFESTATIONS</th>
<th>SYSTEM</th>
<th>MANIFESTATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic</td>
<td>Hypotonia</td>
<td>Facial</td>
<td>Bilateral epicanthal inferior orbital creases</td>
</tr>
<tr>
<td></td>
<td>Floppy-infant syndrome</td>
<td></td>
<td>Palpebral edema</td>
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<tr>
<td></td>
<td>Trismus</td>
<td></td>
<td>Hypertelorism</td>
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<tr>
<td></td>
<td>Strabismus</td>
<td></td>
<td>Coarse facies</td>
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<tr>
<td></td>
<td>Opisthotonus</td>
<td></td>
<td>Low-set ears</td>
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<tr>
<td></td>
<td>Spasticity</td>
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<tr>
<td></td>
<td>Seizures</td>
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<tr>
<td></td>
<td>Peripheral neuropathy</td>
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<tr>
<td></td>
<td>Developmental delay</td>
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<tr>
<td></td>
<td>Irritability</td>
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<tr>
<td></td>
<td>Extrapyramidal movement disorder</td>
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<tr>
<td></td>
<td>Hydrocephalus</td>
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<td></td>
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<tr>
<td>Respiratory</td>
<td>Congenital lobar emphysema</td>
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<tr>
<td></td>
<td>Recurrent respiratory infections</td>
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<td></td>
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<tr>
<td></td>
<td>Hoarseness</td>
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<tr>
<td>Endocrine</td>
<td>Osteopenia</td>
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<tr>
<td></td>
<td>Metabolic bone disease</td>
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<tr>
<td></td>
<td>Secondary hyperparathyroidism</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Congenital adrenal hyperplasia</td>
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<tr>
<td>Cardiovascular</td>
<td>Cardiomegaly</td>
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<tr>
<td></td>
<td>Congenital heart failure</td>
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<tr>
<td></td>
<td>Arrhythmias</td>
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<tr>
<td></td>
<td>Wolff-Parkinson-White syndrome</td>
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<td></td>
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<tr>
<td></td>
<td>Cardiomyopathy</td>
<td></td>
<td></td>
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<tr>
<td>Dysmorphology</td>
<td>Head and neck</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Macrocephaly</td>
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<tr>
<td></td>
<td>Enlarged nuchal translucency</td>
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<tr>
<td></td>
<td>Microstomia</td>
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<tr>
<td></td>
<td>Micrognathia/microretrognathia</td>
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<tr>
<td></td>
<td>Long philtrum</td>
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<tr>
<td></td>
<td>Bilateral broad thumbs and toes</td>
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<tr>
<td></td>
<td>Bilateral club feet</td>
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<td></td>
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<tr>
<td>Limbs</td>
<td>Molar hypoplasia</td>
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<td></td>
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<tr>
<td>Oral</td>
<td>Macroglossia</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Molar hypoplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertrophic gums</td>
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</tbody>
</table>


hydrocephalus, may develop. In the 2nd yr of life, seizures develop which may be refractory to anticonvulsant therapy. Neurodegeneration is relentless, with death occurring by the age of 4 or 5 yr. The juvenile and later-onset forms initially present with ataxia and dystonia and may not be associated with a macular cherry-red spot. The clinical manifestations of Sandhoff disease are similar to those of Tay-Sachs disease. Infants with Sandhoff disease have hepatosplenomegaly, cardiac involvement, and mild bony abnormalities. The juvenile form of this disorder presents as ataxia, dystonia, and mental deterioration, but without visceral enlargement or a macular cherry red spot. There is no treatment available for Tay-Sachs disease or Sandhoff disease, although experimental approaches are being evaluated.

The diagnosis of infantile Tay-Sachs disease and Sandhoff disease is usually suspected in an infant with neurologic features and a cherry-red spot. Definitive diagnosis is made by determination of β-hexosaminidase A and B activities in peripheral leukocytes. The 2 disorders are distinguished by the enzymatic assay, because in Tay-Sachs disease only the β-hexosaminidase A isozyme is deficient, whereas in Sandhoff disease both of the β-hexosaminidase A and B isozymes are deficient. At-risk pregnancies for both disorders can be prenatally diagnosed by determining the enzyme levels in fetal cells obtained by amniocentesis or chorionic villus sampling. Identification of carriers in families is also possible by β-hexosaminidases A and B determination. Indeed, for Tay-Sachs disease, carrier screening of all couples in which at least 1 member is of Ashkenazi Jewish descent is recommended before the initiation of pregnancy to identify couples at risk. These studies can be conducted by the determination of the level of β-hexosaminidase A activity in peripheral leukocytes or plasma.

Molecular studies to identify the exact molecular defect in enzymatically identified carriers should also be performed to permit more specific identification of carriers in the family and to allow prenatal diagnosis in at-risk couples by both enzymatic and genotype determinations. The incidence of Tay-Sachs disease has been markedly reduced since the introduction of carrier screening programs in the Ashkenazi Jewish population. Newborn screening may be possible by measuring specific glycosphingolipid markers, or the relevant enzymatic activities in dried blood spots.

**GAUCHER DISEASE**

This disease is a multisystemic lipidosis characterized by hematologic abnormalities, organomegaly, and skeletal involvement, the latter usually manifesting as bone pain and pathologic fractures (see Table 86-15). It is one of the most common lysosomal storage diseases and the most prevalent genetic defect among Ashkenazi Jews. There are 3 clinical subtypes delineated by the absence or presence and progression of neurologic manifestations: type 1 or the adult, nonneuronopathic form; type 2, the infantile or acute neuronopathic form; and type 3, the juvenile or subacute neuronopathic form. All are autosomal recessive traits. Type 1, which accounts for 99% of cases, has a striking predilection for Ashkenazi Jews, with an incidence of approximately 1 in 1,000 live births and a carrier frequency of approximately 1 in 18 adults.

Gaucher disease results from the deficient activity of the lysosomal hydrolase, acid β-glucosidase, which is encoded by a gene located on chromosome 1q21-q31. The enzymatic defect results in the
Figure 86-15 Pathways in the metabolism of sphingolipids found in nervous tissues. The name of the enzyme catalyzing each reaction is given with the name of the substrate that it hydrolyzes. Inborn errors are depicted as bars crossing the reaction arrows, and the name of the associated defect or defects is given in the nearest box. The gangliosides are named according to the nomenclature of Svennerholm. Anomeric configurations are given only at the largest starting compound. Gal, galactose; glc, glucose; NAcgal, N-acetylgalactosamine; NANA, N-acetylenuraminic acid; PC, phosphorylcholine.

accumulation of undegraded glycolipid substrates, particularly glucosylceramide, in cells of the reticuloendothelial system. This progressive deposition results in infiltration of the bone marrow, progressive hepatosplenomegaly, and skeletal complications. Four mutations—N370S, L444P, 84insG, and IVS2+2—account for approximately 95% of mutant alleles among Ashkenazi Jewish patients, permitting screening for this disorder in this population. Genotype–phenotype correlations have been noted, providing the molecular basis for the clinical heterogeneity seen in Gaucher disease type 1. Patients who are homozygous for the N370S mutation tend to have later onset, with a more indolent course than patients with 1 copy of N370S and another common allele.

Clinical manifestations of type 1 Gaucher disease have a variable age at onset, from early childhood to late adulthood, with most symptomatic patients presenting by adolescence. At presentation, patients may have bruising from thrombocytopenia, chronic fatigue secondary to anemia, hepatosplenomegaly with or without elevated liver function test results, splenomegaly, and bone pain. Occasional patients have pulmonary involvement at the time of presentation. Patients presenting in the 1st decade frequently are not Jewish and have growth retardation and a more malignant course. Other patients may be discovered fortuitously during evaluation for other conditions or as part of routine examinations; these patients may have a milder or even a benign course. In symptomatic patients, splenomegaly is progressive and can become massive. Most patients develop radiologic evidence of skeletal involvement, including an Erlenmeyer flask deformity of the distal femur. Clinically apparent bony involvement, which occurs in most patients, can present as bone pain, a pseudoosteoarthritis pattern or pathologic fractures. Lytic lesions can develop in the long bones, including the femur, ribs, and pelvis; osteosclerosis may be evident at an early age. Bone crises with severe pain and swelling can occur. Bleeding secondary to thrombocytopenia may manifest as epistaxis or bruising and is frequently overlooked until other symptoms become apparent. With the exception of the severely growth-retarded child, who may experience developmental delay secondary to the effects of chronic disease, development and intelligence are normal.

The pathologic hallmark of Gaucher disease is the Gaucher cell in the reticuloendothelial system, particularly in the bone marrow (Fig. 86-18). These cells, which are 20-100 µm in diameter, have a characteristic wrinkled paper appearance resulting from the presence of intracytoplasmic substrate inclusions. The cytoplasm of the Gaucher cell reacts strongly positive with the periodic acid–Schiff stain. The presence of this cell in bone marrow and tissue specimens is highly suggestive of Gaucher disease, although it also may be found in patients with granulocytic leukemia and myeloma.

Gaucher disease type 2 is a rare form and does not have an ethnic predilection. It is characterized by a rapid neurodegenerative course with extensive visceral involvement and death within the first years of life. It presents in infancy with increased tone, strabismus, and organomegaly. Failure to thrive and stridor caused by laryngospasm are typical. After a several-year period of psychomotor regression, death typically occurs secondary to respiratory compromise. Gaucher disease type 3 presents with clinical manifestations that are intermediate to those seen in types 1 and 2, with presentation in childhood
and death by age 10-15 yr. It has a predilection for the Swedish norrbottnian population, among whom the incidence is approximately 1 in 50,000. Neurologic involvement is present. Type 3 disease is further classified as types 3a and 3b based on the extent of neurologic involvement and whether there is progressive myotonia and dementia (type 3a) or isolated supranuclear gaze palsy (type 3b).

Gaucher disease should be considered in the differential diagnosis of patients with unexplained organomegaly, who bruise easily, have bone pain, or have a combination of these conditions. Bone marrow examination usually reveals the presence of Gaucher cells. All suspected diagnoses should be confirmed by determination of the acid β-glucosidase activity and/or the specific family mutations in chorionic villi or cultured amniotic fluid cells. Prenatal diagnosis is available by determination of enzyme activity and whether there is progressive myotonia and dementia (type 3a) or isolated supranuclear gaze palsy (type 3b).

Although enzyme replacement does not alter the neurologic progression of patients with Gaucher disease types 2 and 3, it has been used in selected patients as a palliative measure, particularly in type 3 patients with severe visceral involvement. Alternative treatments, including the use of oral substrate reduction agents designed to decrease the synthesis of glucosylceramide by chemical inhibition of glucosylceramide synthase (e.g., miglustat), also are available. A small number of patients have undergone bone marrow transplantation (BMT), which is curative but is associated with significant morbidity and mortality from the procedure, limiting the selection of appropriate candidates.

**NIEMANN-PICK DISEASE**

The original description of NPD was what is now known as type A NPD, a fatal disorder of infancy characterized by failure to thrive, hepatosplenomegaly, and a rapidly progressive neurodegenerative course that leads to death by 2-3 yr of age. Type B disease is a non-neuronopathic form observed in children and adults. Type C disease is a neuronopathic form that results from defective cholesterol transport. All subtypes are inherited as autosomal recessive traits and display variable clinical features (see Table 86-15).

NPD types A and B result from the deficient activity of acid sphingomyelinase, a lysosomal enzyme encoded by a gene on chromosome
moderate lymphadenopathy, and psychomotor retardation are evident by 6 mo of age, followed by neurodevelopmental regression and death by 3 yr. With advancing age, the loss of motor function and the deterioration of intellectual capabilities are progressively debilitating; and in later stages, spasticity and rigidity are evident. Affected infants lose contact with their environment. In contrast to the stereotyped type A phenotype, the clinical presentation and course of patients with type B disease are more variable. Most are diagnosed in infancy or childhood when enlargement of the liver or spleen, or both, is detected during a routine physical examination. At diagnosis, type B NPD patients usually have evidence of mild pulmonary involvement, usually detected as a diffuse reticular or finely nodular infiltration on the chest radiograph. Pulmonary symptoms may present in adults. In most patients, hepatosplenomegaly is particularly prominent in childhood, but with increasing linear growth, the abdominal protuberance decreases and becomes less conspicuous. In mildly affected patients, the splenomegaly may not be noted until adulthood, and there may be minimal disease manifestations. Severely affected patients may have liver involvement leading to life-threatening cirrhosis, portal hypertension, and ascites. Clinically significant pancytopenia caused by secondary hypersplenism may require partial or complete splenectomy; this should be avoided if possible because splenectomy frequently causes progression of pulmonary disease, which can be life-threatening. In general, type B patients do not have neurologic involvement and have a normal IQ. Some patients with type B disease have cherry-red maculae or haloes and subtle neurologic symptoms (peripheral neuropathy). In some type B patients, decreased pulmonary diffusion caused by alveolar infiltration becomes evident in late childhood or early adulthood and progresses with age.

Figure 86-17 Algorithm of the clinical evaluation recommended for an infant with a suspected lysosomal storage disease. GAGs, glycosaminoglycans; NIHF, nonimmune hydrops fetalis. (From Staretz-Chacham O, Lang TC, LaMarca ME, et al: Lysosomal storage disorders in the newborn, Pediatrics 123:1191–1207, 2009.)

Figure 86-18 Cells from the spleen of a patient with Gaucher disease. A characteristic spleen cell is shown engorged with glucocerebrosidase.
Severely affected individuals may experience significant pulmonary compromise by 15-20 yr of age. Such patients have low PO₂ values and dyspnea on exertion. Life-threatening bronchopneumonias may occur, and cor pulmonale has been described.

Type C NPD patients often present with prolonged neonatal jaundice, appear normal for 1-2 yr, and then experience a slowly progressive and variable neurodegenerative course. Their hepatosplenomegaly is less severe than that of patients with types A or B NPD, and they may survive into adulthood. The underlying biochemical defect in type C patients is an abnormality in cholesterol transport, leading to the accumulation of sphingomyelin and cholesterol in their lysosomes and a secondary partial reduction in acid sphingomyelinase activity (see Chapter 86.3).

In type B NPD patients, splenomegaly is usually the first manifestation detected. The splenic enlargement is noted in early childhood; in very mild disease, the enlargement may be subtle and detection may be delayed until adolescence or adulthood. The presence of the characteristic NPD cells in bone marrow aspirates supports the diagnosis of type B NPD. Patients with type C NPD, however, also have extensive infiltration of NPD cells in the bone marrow and, thus, all suspected cases should be evaluated enzymatically to confirm the clinical diagnosis by measuring the acid sphingomyelinase activity level in peripheral leukocytes, cultured fibroblasts, or lymphoblasts, or a combination of these cells. Patients with types A and B NPD have markedly decreased levels (1-10%), whereas patients with type C NPD have normal or somewhat decreased acid sphingomyelinase activities. The enzymatic identification of NPD carriers is problematic. In families in which the specific molecular lesion has been identified, however, family members can be accurately tested for heterozygote status by DNA analysis. Prenatal diagnosis of types A and B NPD can be made reliably by the measurement of acid sphingomyelinase activity in cultured amniocytes or chorionic villi; molecular analysis of fetal cells to identify the specific acid sphingomyelinase mutations can provide the specific diagnosis or serve as a confirmatory test. The clinical diagnosis of type C NPD can be supported by the demonstration of filipin stain positivity in cultured fibroblasts and/or by identifying a specific mutation in the NPC 1 or 2 gene.

Currently there is no specific treatment for NPD. Orthotopic liver transplantation in an infant with type A disease and cord blood transplantation in several type B NPD patients have been attempted with little or no success. BMT in a small number of type B NPD patients has been successful in reducing the spleen and liver volumes, the sphingomyelin content of the liver, the number of Niemann-Pick cells in the marrow, and radiologically detected infiltration of the lungs. In 1 patient, liver biopsies taken up to 33 mo posttransplantation showed only a moderate reduction in stored sphingomyelin. A phase I trial of enzyme replacement therapy for type B NPD has been completed which demonstrated elevated cytokine and bilirubin levels at the higher doses administered (0.6 and 1.0 mg/kg). The observed toxicity is presumably a result of the catabolism of the accumulated sphingomyelin to ceramide. Further clinical studies to evaluate effectiveness of this approach are planned. Clinical trials of miglustat (Actelion, Basel, Switzerland) have been performed and the drug has been approved in Europe for the treatment of type C disease. Treatment of type A disease by BMT has not been successful presumably because of the severe neurologic involvement.

**FABRY DISEASE**

This disease is an X-linked inborn error of glycosphingolipid metabolism caused by the absent or markedly deficient activity of α-galactosidase A (α-gal A). There are 2 major phenotypes. Affected males with the classic phenotype present in childhood with angiokeratomas (telangiectatic skin lesions), hypohidrosis, corneal and lenticular opacities, acroparesthesias, and with advancing age develop vascular disease of the kidney, heart, and/or brain (see Table 86-13). This classic phenotype is caused by the absent activity of the α-gal A and has an estimated prevalence of approximately 1 in 50,000 males. The later-onset phenotype occurs in affected males with residual α-gal A activity and presents in the 4th to 8th decades with cardiac disease and/or renal failure. This phenotype is more prevalent than the classic phenotype.

Heterozygous females for the classic phenotype can be asymptomatic or as severely affected as the males, the variability a result of random X-inactivation. The enzyme deficiency results from mutations in the α-gal A gene located on the long arm of the X chromosome (Xq22). The enzymatic defect leads to the systemic accumulation of neutral glycosphingolipids, primarily globotriaosylceramide, particularly in the plasma and lysosomes of vascular endothelial and smooth muscle cells, cardiac myocytes, and renal podocytes. The progressive vascular glycosphingolipid deposition in classically affected males results in small vessel occlusion and ischemia, leading to the major disease manifestations. The complementary DNA and genomic sequences encoding α-gal A have been characterized and more than 500 different mutations in the α-gal A gene are responsible for this lysosomal storage disease.

The **angiokeratomas** usually occur in childhood and may lead to early diagnosis (Fig. 86-19). They increase in size and number with age and range from barely visible to several millimeters in diameter. The lesions are punctate, dark red to blue-black, and flat or slightly raised. They do not blanch with pressure, and the larger ones may show slight hyperkeratosis. Characteristically, the lesions are most dense between the umbilicus and knees, in the “bathing trunk area,” but may occur anywhere, including the oral mucosa. The hips, thighs, buttocks, umbilicus, lower abdomen, scrotum, and glans penis are common sites, and there is a tendency toward symmetry. Variants without skin lesions have been described. Sweating is usually decreased or absent. Corneal opacities and characteristic lenticular lesions, observed under slit-lamp examination, are present in affected males, as well as in approximately 90% of heterozygotes from families with the classic phenotype. Conjunctival and retinal vascular tortuosity is common and results from the systemic vascular involvement.

**Pain** is the most debilitating symptom in childhood and adolescence. **Fabry crises**, lasting from minutes to several days, consist of agonizing, burning pain in the hands, feet, and proximal extremities and are usually associated with exercise, fatigue, fever, or a combination of these factors. These painful acroparesthesias usually become less frequent in the 3rd and 4th decades of life, although in some men, they may become more frequent and severe. Attacks of abdominal or flank pain may simulate appendicitis or renal colic.

The major morbid symptoms result from the progressive involvement of the vascular system. Early in the course of the classic phenotype, casts, red cells, and lipid inclusions with characteristic birefringent “Maltese crosses” appear in the urinary sediment. Proteinuria, isothesisuria, and gradual deterioration of renal function and development of azotemia occur in the 2nd through 4th decades in the classic phenotype and in the 4th to 8th decades in the later-onset form. Cardiovascular findings may include arrhythmias, left ventricular hypertrophy, angina, myocardial ischemia or infarction, and heart failure. Mitral insufficiency is the most common valvular lesion. Cerebrovascular
manifestations, including transient ischemic attacks and strokes, result from multifocal small vessel involvement. Other features may include chronic bronchitis and dyspnea, lymphedema of the legs without hypoproteinemia, episodic diarrhea, osteoporosis, retarded growth, and delayed puberty. Death most often results from renal failure or vascular disease of the heart or brain. Before hemodialysis or renal transplantation, the mean age at death for affected men was 40 yr. Patients with the later-onset phenotype with residual α-gal A activity have cardiac and/or renal disease. The cardiac manifestations include hypertrophy of the left ventricular wall and interventricular septum, and electrocardiographic abnormalities consistent with cardiomyopathy. Patients may progress to hypertrophic cardiomyopathy or myocardial infarction, or both.

The diagnosis in classically affected males is most readily made from the history of painful acroparesthesias, hypohidrosis, the presence of the characteristic skin lesions, and the observation of the corneal opacities and lenticular lesions. The disorder is often misdiagnosed as rheumatic fever, erythromelalgia, or neurosis. The skin lesions must be differentiated from the benign angiokeratomas of the scrotum (Fordyce disease) or from angiokeratoma circumscriptum. Angiokeratomas identical to those of Fabry disease have been reported in fucosidosis, aspartylglycosaminuria, late-onset GM1 gangliosidosis, galactosialidosis, α-N-acetylgalactosaminidase deficiency, and sialidosis. Later-onset patients have been identified among patients on hemodialysis and among patients with hypertrophic cardiomyopathy or who have suffered cryptogenic strokes. Later-onset patients lack the early classic manifestations such as the angiokeratomas, acroparesthesias, hypohidrosis, and corneal opacities. The diagnosis of classic and later-onset patients is confirmed biochemically by the demonstration of markedly decreased α-gal A activity in plasma, isolated leukocytes, or cultured fibroblasts or lymphoblasts. The specific α-gal A mutation can be determined by gene sequencing.

Heterozygous females may have corneal opacities, isolated skin lesions, and intermediate activities of α-gal A in plasma or cells. Rare female heterozygotes may have manifestations as severe as those in affected males. Asymptomatic at-risk females in families affected by Fabry disease, however, should be optimally diagnosed by the direct analysis of their family's specific mutation. Prenatal detection of affected males can be accomplished by the demonstration of deficient α-gal A activity and/or the family's specific gene mutation in chorionic villi obtained in the 1st trimester or in cultured amniocytes obtained by amniocentesis in the 2nd trimester of pregnancy. Fabry disease can be detected by newborn screening and pilot studies have been conducted in Italy and Taiwan.

Treatment for Fabry disease may include the use of phenytoin and/or carbamazepine to decrease the frequency and severity of the chronic acroparesthesias and the periodic crises of excruciating pain. Renal transplantation and long-term hemodialysis are lifesaving procedures for patients with renal failure.

Enzyme replacement therapy for Fabry patients using recombinant human α-gal A preparations produced in Chinese hamster ovary cells (agalsidase beta, Fabrazyme, Genzyme Corporation) and in human fibrosarcoma cells (agalsidase alfa, Replagal, Shire HGT) has been developed. Both Fabrazyme and Replagal were approved by the European Medicines Agency in the European Union, but only Fabrazyme is approved by the FDA in the United States. The effectiveness of enzyme replacement therapy with Fabrazyme in stabilization of renal disease, regression of hypertrophic cardiomyopathy, reduction of pain, and improvement in quality of life has been demonstrated. Because most classically affected males produce no enzyme protein, these patients produce immunoglobulin G antibodies in response to the infused enzyme which can impact the effectiveness of substrate clearance. Treatment of classically affected males should begin in childhood.

FUCOSIDOSIS

This is a rare autosomal recessive disorder caused by the deficient activity of α-fucosidase and the accumulation of fucose-containing glycosphingolipids, glycoproteins, and oligosaccharides in the lysosomes of the liver, brain, and other organs (see Table 86-15). The α-fucosidase gene is on chromosome 1 (1p24), and specific mutations are known. Although the disorder is panethnic, most reported patients are from Italy and the United States. There is wide variability in the clinical phenotype, with the most severely affected patients presenting in the first year of life with developmental delay and somatic features similar to those of the mucopolysaccharidoses. These features include frontal bossing, hepatosplenomegaly, coarse facial features, and macroGLOSSIA. The central nervous system storage results in a relentless neurodegenerative course, with death in childhood. Patients with milder disease have angiod streaks and longer survival. No specific therapy exists for the disorder, which can be diagnosed by the demonstration of deficient α-fucosidase activity in peripheral leukocytes or cultured fibroblasts. Carrier identification and prenatal diagnosis are possible by determination of the enzymatic activity or the specific family mutations.

SCHINDLER DISEASE

This is an autosomal recessive neurodegenerative disorder that results from the deficient activity of α-N-acetylgalactosaminidase and the accumulation of sialylated and asialoglycopeptides and oligosaccharides (see Table 86-15). The gene for the enzyme is located on chromosome 22 (22q11). The disease is clinically heterogeneous, and 2 major phenotypes have been identified. Type I disease is an infantile-onset neuroaxonal dystrophy. Affected infants have normal development for the first 9-15 mo of life followed by a rapid neurodegenerative course that results in severe psychomotor retardation, cortical blindness, and frequent myoclonic seizures. Type II disease is characterized by a variable age at onset, mild intellectual disability, and angiokeratomas. There is no specific therapy for either form of the disorder. The diagnosis is by demonstration of the enzymatic deficiency in leukocytes or cultured skin fibroblasts or specific gene mutations.

METACHROMATIC LEUKODYSTrophy

This is an autosomal recessive white matter disease caused by a deficiency of arylsulfatase A (ASA), which is required for the hydrolysis of sulfated glycosphingolipids. Another form of metachromatic leukodystrophy (MLD) is caused by a deficiency of a sphingolipid activator protein (SAP1), which is required for the formation of the substrate–enzyme complex. The deficiency of this enzymatic activity results in the white matter storage of sulfated glycosphingolipids, which leads to demyelination and a neurodegenerative course. The ASA gene is on chromosome 22 (22q13.31qter); specific mutations tend to fall into 2 groups that correlate with disease severity.

The clinical manifestations of the late infantile form of MLD, which is most common, usually present between 12 and 18 mo of age as irritability, inability to walk, and hypotonia, which may be profound in affected males. Asymptomatic at-risk females in families affected by Fabry disease, however, should be optimally diagnosed by the direct analysis of their family's specific mutation. Prenatal detection of affected males can be accomplished by the demonstration of deficient α-gal A activity and/or the family's specific gene mutation in chorionic villi obtained in the 1st trimester or in cultured amniocytes obtained by amniocentesis in the 2nd trimester of pregnancy. Fabry disease can be detected by newborn screening and pilot studies have been conducted in Italy and Taiwan.

Treatment for Fabry disease may include the use of phenytoin and/or carbamazepine to decrease the frequency and severity of the chronic acroparesthesias and the periodic crises of excruciating pain. Renal transplantation and long-term hemodialysis are lifesaving procedures for patients with renal failure.

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FUCOSIDOSIS

This is a rare autosomal recessive disorder caused by the deficient activity of α-fucosidase and the accumulation of fucose-containing glycosphingolipids, glycoproteins, and oligosaccharides in the lysosomes of the liver, brain, and other organs (see Table 86-15). The α-fucosidase gene is on chromosome 1 (1p24), and specific mutations
sediment are all suggestive of MLD. Confirmation of the diagnosis is based on the demonstration of the reduced activity of ASA in leukocytes or cultured skin fibroblasts. SAP deficiency is diagnosed by measuring the concentration of SAP1 in cultured fibroblasts using a specific antibody to the protein. The diagnosis, identification of carriers and prenatal diagnosis are available for both forms of the disorder by detection of the causative mutations in the ASA or SAP genes.

Unrelated donor umbilical cord blood transplantation has been undertaken in some pediatric patients with MLD. A longitudinal study of 6 patients with late-infantile onset and 14 with juvenile onset revealed that motor deficits present at the time of transplant did not improve and that neurologic symptoms continued to progress in those with late-infantile presentation. In contrast, in juvenile patients the brainstem auditory evoked responses, visual evoked potentials, electroencephalogram, and/or peripheral nerve conduction velocities stabilized or improved. Therefore consideration of umbilical cord blood transplantation for children with presymptomatic late-infantile MLD or minimally symptomatic juvenile MLD may be indicated.

**MULTIPLE SULFATASE DEFICIENCY**

This is an autosomal recessive disorder that results from the enzymatic deficiency of at least 9 sulfatases including arylsulfatases A, B, and C, and idurionate-2-sulfatase. The specific defect is an enzyme in the C-α-formylglycine generating system (the gene for which is located at 3p26), which introduces a common posttranslational modification in all of the affected sulfatases and explains the occurrence of these multiple enzyme defects. Because of the deficiency of these enzymes, sulfatides, mucopolysaccharides, steroid sulfates, and gangliosides accumulate in the cerebral cortex and visceral tissues, resulting in a clinical phenotype with features of a leukodystrophy as well as those of the mucopolysaccharidoses. Severe ichthyosis may also occur. Carrier testing and prenatal diagnosis by measurement of the enzymatic activities or the specific gene defects can be performed. There is no specific treatment for multiple sulfatase deficiency other than supportive care.

**KRABBE DISEASE**

This condition, also called globoid cell leukodystrophy, is an autosomal recessive fatal disorder of infancy. It results from the deficient activity of galactocerebroside and the white matter accumulation of galactosylceramide, which is normally found almost exclusively in the myelin sheath. Both peripheral and central myelin are affected, resulting in spasticity and cognitive impairment coupled with deceptively normal or even absent deep tendon reflexes. The galactocerebroside gene is on chromosome 14 (14q31), and specific disease-causing mutations are known. The infantile form of Krabbe disease is rapidly progressive and patients present in early infancy with irritability, seizures, and hypertonia (see Table 86-15). Optic atrophy is evident in the 1st yr of life, and mental development is severely impaired. As the disease progresses, optic atrophy and severe developmental delay become apparent; affected children exhibit opisthotonos and die before 3 yr of age. A late infantile form of Krabbe presents after the age of 2 yr. Affected individuals have a course similar to that of the early infantile form.

The diagnosis of Krabbe disease relies on the demonstration of the specific enzymatic deficiency in white blood cells or cultured skin fibroblasts. Causative gene mutations have been identified. Carrier identification and prenatal diagnosis are available. The development of methods to measure galactocerebroside activity on dried blood spots has led to the inclusion of Krabbe disease in the newborn screening programs of some states. Treatment of infants with Krabbe disease with umbilical cord blood cell transplantation has been reported in prenatally identified asymptomatic newborns and symptomatic infants. Transplanted infants appear to develop neurologic manifestations at a slower rate but succumb to a neurologic demise.

**FARBER DISEASE**

This is a rare autosomal recessive disorder that results from the deficiency of the lysosomal enzyme acid ceramidase and the accumulation of ceramide in various tissues, especially the joints. Symptoms can begin in the first year of life with painful joint swelling and nodule formation (Fig. 86-20), which is sometimes diagnosed as rheumatoid arthritis. As the disease progresses, nodule or granulomatous formation on the vocal cords can lead to hoarseness and breathing difficulties; failure to thrive is common. In some patients, moderate central nervous system dysfunction is present (see Table 86-15). Patients may die of recurrent pneumonias in their teens; there is currently no specific therapy. The diagnosis of this disorder should be suspected in patients who have nodule formation over the joints but no other findings of rheumatoid arthritis. In such patients, ceramidase activity should be determined in cultured skin fibroblasts or peripheral leukocytes. Various disease-causing mutations have been identified in the acid ceramidase gene. Carrier detection and prenatal diagnosis are available.

**WOLMAN DISEASE AND CHOLESTEROL ESTER STORAGE DISEASE**

These are autosomal recessive lysosomal storage diseases that result from the deficiency of acid lipase and the accumulation of cholesterol esters and triglycerides in histiocytic foam cells of most visceral organs. The gene for lysosomal acid lipase is on chromosome 10 (10q24-q25). Wolman disease is the more severe clinical phenotype and is a fatal disorder of infancy. Clinical features become apparent in the first weeks of life and include failure to thrive, relentless vomiting, abdominal distention, steatorrhea, and hepatosplenomegaly (see Table 86-15). There usually is hyperlipidemia. Hepatic dysfunction and fibrosis may occur. Calcification of the adrenal glands occurs in about 50% of patients. Death usually occurs within the first 6 mo of life.

Cholesterol ester storage disease is a less-severe disorder that may not be diagnosed until adulthood. Hepatomegaly can be the only detectable abnormality, but affected individuals are at significant risk for premature cirrhosis and atherosclerosis. Adrenal calcification can occur in severe early onset patients.

Diagnosis and carrier identification are based on measuring acid lipase activity in peripheral leukocytes or cultured skin fibroblasts. Disease causing mutations have been identified in the acid ceramide gene. Prenatal diagnosis depends on measuring decreased enzyme levels or identifying specific mutations in cultured chorionic villi or amnionctyes. There is no specific therapy available for either disorder. Although pharmacologic agents to suppress cholesterol synthesis, in combination with cholestyramine and diet modification, have been used in patients there is little to no clinical benefit. Enzyme
replacement therapy is currently being evaluated in clinical trials for both diseases (see Chapter 86.3).

Bibliography is available at Expert Consult.

86.5 Mucolipidoses

Margaret M. McGovern and Robert J. Desnick

I-cell disease (mucolipidosis II [ML-II]) and pseudo-Hurler polydystrophy (mucolipidosis III [ML-III]) are rare autosomal recessive disorders that share some clinical features with Hurler syndrome (see Chapter 88). These diseases result from the abnormal targeting of newly synthesized lysosomal enzymes that normally have phosphorylated mannose residues for binding to the mannose-6-phosphate receptors which transport the enzymes to the lysosomes. These mannose-6-phosphate residues are synthesized in a 2-step reaction that occurs in the Golgi apparatus and is mediated by 2 enzymatic activities. The enzyme that catalyzes the first step, the lysosomal enzyme N-acetylglucosamine-1-phosphotransferase, is defective in both ML-II and ML-III, which are allelic disorders resulting from mutations in the GlcNAc-phosphotransferase α/β-subunits precursor gene (GNPTAB). This enzyme deficiency results in abnormal targeting of the lysosomal enzymes which are consequently secreted into the extracellular matrix. Because the lysosomal enzymes require the acidic environment of the lysosome to function, patients with this defect accumulate a variety of different substrates because of the intracellular deficiency of most lysosomal enzymes. The diagnosis of ML-II and ML-III can be made by the determination of the serum lysosomal enzymatic activities, which are markedly elevated, or by the demonstration of their reduced enzymatic activity levels in cultured skin fibroblasts. Direct measurement of the phosphotransferase activity is possible as well. Prenatal diagnosis is available for both disorders by measurement of lysosomal enzymatic activities in amniocytes or chorionic villus cells; carrier identification is available for both disorders by measurement of enzymatic activities using cultured skin fibroblasts or by mutation analysis of the causative gene. Neonatal screening by tandem mass spectroscopy may detect I-cell disease.

I-CELL DISEASE

This disorder, ML-II, shares many of the clinical manifestations of Hurler syndrome (see Chapter 88), although there is no mucopolysacchariduria and the presentation is earlier (see Table 86-15). Some patients have clinical features evident at birth, including coarse facial features, craniofacial abnormalities, restricted joint movement, and hypotonia. Nonimmune hydrops may be present in the fetus. The remainder of patients present in the first year with severe psychomotor retardation, coarse facial features, and skeletal manifestations that include kyphoscoliosis and a lumbar gibbus. Patients may also have congenital dislocation of the hips, inguinal hernias, and gingival hypertrophy. Progressive, severe psychomotor retardation leads to death in early childhood. No treatment is available.

PSEUDO-HURLER POLYDYSTROPHY

Pseudo-Hurler polydystrophy (ML-III) is a less-severe disorder than I-cell disease, with later onset and survival to adulthood reported. Affected children may present around the age of 4 or 5 yr with joint stiffness and short stature. Progressive destruction of the hip joints and moderate dysostosis multiplex are evident. Radiographic evidence of low iliac wings, flattening of the proximal femoral epiphyses with valgus deformity of the femoral head, and hypoplasia of the anterior third of the lumbar vertebrae are characteristic findings. Ophthalmic findings include corneal clouding, retinopathy, and astigmatism; visual complaints are uncommon (see Table 86-15). Some patients have learning disabilities or intellectual disability. Treatment, which should include orthopedic care, is symptomatic.

Bibliography is available at Expert Consult.


Bibliography


Bibliography
Defects in Metabolism of Carbohydrates

Chapter 87

Priya S. Kishnani and Yuan-Tsong Chen

Carbohydrate synthesis and degradation provide the energy required for most metabolic processes. The important carbohydrates include 3 monosaccharides—glucose, galactose, and fructose—and a polysaccharide, glycogen. Figure 87-1 shows the relevant biochemical pathways of these carbohydrates. Glucose is the principal substrate of energy metabolism. A continuous source of glucose from dietary intake, gluconeogenesis, and glycogenolysis of glycogen maintains normal blood glucose levels. Metabolism of glucose generates adenosine triphosphate (ATP) via glycolysis (conversion of glucose or glycogen to pyruvate), mitochondrial oxidative phosphorylation (conversion of pyruvate to carbon dioxide and water), or both. Dietary sources of glucose come from ingesting polysaccharides, primarily starch and disaccharides, including lactose, maltose, and sucrose. Oral intake of glucose is intermittent and unreliable. Glucose made de novo from amino acids, primarily alanine (gluconeogenesis), contributes to maintaining the euglycemic state, but this process requires time. The breakdown of hepatic glycogen provides the rapid release of glucose, which maintains a constant blood glucose concentration. Glycogen is also the primary stored energy source in muscle, providing glucose for muscle activity during exercise. Galactose and fructose are monosaccharides that provide fuel for cellular metabolism; their role is less significant than that of glucose. Galactose is derived from lactose (galactose + glucose), which is found in milk and milk products. Galactose is an important energy source in infants, but it is first metabolized to glucose. Galactose (exogenous or endogenously synthesized from glucose) is also an important component of certain glycolipids, glycoproteins, and glycosaminoglycans. The dietary sources of fructose are sucrose (fructose + glucose, sorbitol) and fructose itself, which is found in fruits, vegetables, and honey.

Defects in glycogen metabolism typically cause an accumulation of glycogen in the tissues, hence the name glycogen storage disease (Table 87-1). Defects in gluconeogenesis or the glycolytic pathway, including galactose and fructose metabolism, do not result in an accumulation of glycogen (Table 87-1). The defects in pyruvate metabolism in the pathway of the conversion of pyruvate to carbon dioxide and water via mitochondrial oxidative phosphorylation are more often associated with lactic acidosis and some tissue glycogen accumulation.

87.1 Glycogen Storage Diseases

Priya S. Kishnani and Yuan-Tsong Chen

The disorders of glycogen metabolism, the glycogen storage diseases (GSDs), result from deficiencies of various enzymes or transport proteins in the pathways of glycogen metabolism (see Fig. 87-1). The glycogen found in these disorders is abnormal in quantity, quality, or both. GSDs are categorized by numeric type in accordance with the chronological order in which these enzymatic defects were identified. This numeric classification is still widely used, at least up to number VII. The GSDs can also be classified by organ involvement and clinical manifestations into liver and muscle glycogenoses (see Table 87-1).

There are more than 12 forms of glycogenoses. Glucose-6-phosphatase deficiency (type I), lysosomal acid α-glucosidase deficiency (type II), debrancher deficiency (type III), and liver phosphorylase kinase
deficiency (type IX) are the most common of those that typically present in early childhood; myophosphorylase deficiency (type V, McArdle disease) is the most common in adolescents and adults. The frequency of all forms of GSD is approximately 1 in 20,000 live births.

**LIVER GLYCOGENOSIS**

The GSDs that principally affect the liver include glucose-6-phosphatase deficiency (type I), debranching enzyme deficiency (type III), branching enzyme deficiency (type IV), liver phosphorylase deficiency (type VI), phosphorylase kinase deficiency (type IX, formerly termed GSD VIa), glycogen synthase deficiency (type 0), and glucose transporter-2 defect. Because hepatic carbohydrate metabolism is responsible for plasma glucose homeostasis, this group of disorders typically causes fasting hypoglycemia and hepatomegaly. Some (types III, IV, IX) can be associated with liver cirrhosis. Other organs can also be involved and may manifest as renal dysfunction in type I, myopathy (skeletal and/or cardiomyopathy) in types III and IV, as well as in some rare forms of phosphorylase kinase deficiency, and neurologic involvement in types II (the brain, anterior horns cells), III (peripheral nerves), and IV (some patients can present with diffuse central and peripheral nervous system dysfunction).

**Type I Glycogen Storage Disease (Glucose-6-Phosphatase or Translocase Deficiency, Von Gierke Disease)**

Type I GSD is caused by the absence or deficiency of glucose-6-phosphatase activity in the liver, kidney, and intestinal mucosa. It can be divided into 2 subtypes: type Ia, in which the glucose-6-phosphatase
<table>
<thead>
<tr>
<th>DISORDERS</th>
<th>BASIC DEFECTS</th>
<th>CLINICAL PRESENTATION</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LIVER GLYCOGENOSES</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Type/Common Name</td>
<td></td>
<td></td>
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<tr>
<td>Ia/Von Gierke</td>
<td>Glucose-6-phosphatase</td>
<td>Growth retardation, hepatomegaly, hypoglycemia; elevated blood lactate, cholesterol, triglyceride, and uric acid levels</td>
<td>Common, severe hypoglycemia</td>
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<td>Ib</td>
<td>Glucose-6-phosphate translocase</td>
<td>Same as type Ia, with additional findings of neutropenia and impaired neutrophil function</td>
<td>10% of type Ia</td>
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<td>Illa/Cori or Forbes</td>
<td>Liver and muscle debrancher deficiency (amylo-1,6-glucosidase)</td>
<td>Childhood: hepatomegaly, growth retardation, muscle weakness, hypoglycemia, hyperlipidemia, elevated transaminase levels; liver symptoms can progress to liver failure later in life</td>
<td>Common, intermediate severity of hypoglycemia</td>
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<tr>
<td>Illb</td>
<td>Liver debrancher deficiency; normal muscle enzyme activity</td>
<td>Liver symptoms same as in type Illa; no muscle symptoms</td>
<td>15% of type III</td>
</tr>
<tr>
<td>IV/Andersen</td>
<td>Branching enzyme</td>
<td>Failure to thrive, hypotonia, hepatomegaly, splenomegaly, progressive cirrhosis (death usually before 5th yr), elevated transaminase levels</td>
<td>Rare neuromuscular variants exist</td>
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<tr>
<td>VI/Hers</td>
<td>Liver phosphorylase</td>
<td>Hepatomegaly, typically mild hypoglycemia, hyperlipidemia, and ketosis</td>
<td>Rare, typically benign glycogenosis; severe presentation also known</td>
</tr>
<tr>
<td>Phosphorylase kinase deficiency</td>
<td>Phosphorylase kinase</td>
<td>Hepatomegaly, mild hypoglycemia, hyperlipidemia, and ketosis</td>
<td>Common, typically a benign glycogenosis, severe progressive forms also present</td>
</tr>
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<td>Glycogen synthase deficiency</td>
<td>Glycogen synthase</td>
<td>Early morning drowsiness and fatigue, fasting hypoglycemia, and ketosis, no hepatomegaly</td>
<td>Decreased liver glycogen store</td>
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<td>Fanconi-Bickel syndrome</td>
<td>Glucose transporter 2 (GLUT-2)</td>
<td>Failure to thrive, rickets, hepatorenalopathy, proximal renal tubular dysfunction, impaired glucose and galactose utilization</td>
<td>GLUT-2 expressed in liver, kidney, pancreas, and intestine</td>
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<td><strong>MUSCLE GLYCOGENOSES</strong></td>
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<td>Type/Common Name</td>
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<td>II/Pompe infantile</td>
<td>Acid α-glucosidase (acid maltase)</td>
<td>Cardiomegaly, hypotonia, hepatomegaly; onset: birth to 6 mo</td>
<td>Common, cardiorespiratory failure leading to death by age 1-2 yr; minimal to no residual enzyme activity</td>
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<td>II/Late-onset Pompe (juvenile and adult) Danon disease</td>
<td>Acid α-glucosidase (acid maltase) Lysosome-associated membrane protein 2 (LAMP2)</td>
<td>Myopathy, variable cardiomyopathy, respiratory insufficiency; onset: childhood to adulthood</td>
<td>Residual enzyme activity</td>
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<td>PRKAG2 deficiency</td>
<td>Adenosine monophosphate (AMP)-activated protein kinase γ</td>
<td>Hypertrophic cardiomyopathy</td>
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<td>V/McArdle</td>
<td>Myophosphorylase</td>
<td>Exercise intolerance, muscle cramps, increased fatigability</td>
<td>Common, male predominance</td>
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<td>VII/Tarui</td>
<td>Phosphofructokinase</td>
<td>Exercise intolerance, muscle cramps, hemolytic anemia, myoglobinuria</td>
<td>Prevalent in Japanese and Ashkenazi Jews</td>
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<td>Phosphoglycerate kinase deficiency</td>
<td>Phosphoglycerate kinase</td>
<td>As with type V</td>
<td>Rare, X-linked</td>
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<td>Phosphoglycerate mutase deficiency</td>
<td>M subunit of phosphoglycerate mutase</td>
<td>As with type V</td>
<td>Rare, majority of patients are African-American</td>
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<tr>
<td>Lactate dehydrogenase deficiency</td>
<td>M subunit of lactate dehydrogenase</td>
<td>As with type V</td>
<td>Rare</td>
</tr>
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<td><strong>GALACTOSE DISORDERS</strong></td>
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<tr>
<td>Galactosemia with transferase deficiency</td>
<td>Galactokinase</td>
<td>Vomiting, hepatomegaly, cataracts, aminoaciduria, failure to thrive Cataracts</td>
<td>African-American patients tend to have milder symptoms</td>
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<td>Galactokinase deficiency</td>
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<td>Benign</td>
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<tr>
<td>Generalized uridine diphosphate galactose-4-epimerase deficiency</td>
<td>Uridine diphosphate galactose-4-epimerase</td>
<td>Similar to transferase deficiency with additional findings of hypotonia and nerve deafness</td>
<td>A benign variant also exists</td>
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<td><strong>FRUCTOSE DISORDERS</strong></td>
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<td>Essential fructosuria</td>
<td>Fructokinase</td>
<td>Urine reducing substance</td>
<td>Benign</td>
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<td>Hereditary fructose intolerance</td>
<td>Fructose-1-phosphate aldolase</td>
<td>Acute: vomiting, sweating, lethargy</td>
<td>Prognosis good with fructose restriction</td>
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enzyme is defective; and type Ib, in which a translocase that transports glucose-6-phosphate across the microsomal membrane is defective. The defects in both type Ia and type Ib lead to inadequate hepatic conversion of glucose-6-phosphate to glucose through normal glycogenolysis and gluconeogenesis and make affected individuals susceptible to fasting hypoglycemia. Type I GSD is an autosomal recessive disorder. The structural gene for glucose-6-phosphatase is located on chromosome 17q21; the gene for the translocase is on chromosome 11q23. Common mutations responsible for the disease are known. Carrier detection and prenatal diagnosis are possible with the DNA-based diagnosis.

**Clinical Manifestations**

Patients with type I GSD may present in the neonatal period with hypoglycemia and lactic acidosis; they more commonly present at 3–4 mo of age with hepaticomegaly, hypoglycemic seizures, or both. These children often have “doll-like faces” with fat cheeks, relatively thin extremities, short stature, and a protuberant abdomen that is a consequence of massive hepatomegaly; the kidneys are also enlarged, whereas the spleen and heart are normal.

The *biochemical hallmarks* of the disease are hypoglycemia, lactic acidosis, hyperuricemia, and hyperlipidemia. Hypoglycemia and lactic acidosis can develop after a short fast. Hyperuricemia is present in young children; gout rarely develops before puberty. Despite marked hepatomegaly, the liver transaminase levels are usually normal or only slightly elevated. Intermittent diarrhea may occur in GSD I. In patients with GSD Ib, the loss of mucosal barrier function as a result of inflammation, which is likely related to the disturbed neutrophil function, seems to be the main cause of diarrhea. Easy bruising and epistaxis are common and are associated with a prolonged bleeding time as a result of impaired platelet aggregation and adhesion.

The plasma may be “milky” in appearance as a result of a striking elevation of triglyceride levels. Cholesterol and phospholipids are also elevated, but less prominently. The lipid abnormality resembles type IV hyperlipidemia and is characterized by increased levels of very-low-density lipoprotein, low-density lipoprotein, and a unique apolipoprotein profile consisting of increased levels of apolipoproteins B, C, and E, with relatively normal or reduced levels of apolipoproteins A and D. The histologic appearance of the liver is characterized by a universal distention of hepatocytes by glycogen and fat. The lipid vacuoles are particularly large and prominent. There is little associated fibrosis. All these findings apply to both type Ia and type Ib GSD, but type Ib has additional features of recurrent bacterial infections from neutropenia and impaired neutrophil function. Gut mucosa ulceration culminating in GSD enterocolitis is also common. Exceptional cases of type Ib without neutropenia and type Ia with neutropenia have been reported.

Although type I GSD affects mainly the liver, multiple organ systems are involved. Puberty is often delayed. Females can have ultrasound findings consistent with polycystic ovaries; other features of polycystic ovary syndrome (acne, hirsutism) are not seen. Nonetheless, fertility appears to be normal, as evidenced in several reports of successful pregnancy in women with GSD I. Increased bleeding during menstrual cycles, including life-threatening menorrhagia, has been noted and could be related to the impaired platelet aggregation. Symptoms of gout usually start around puberty from long-term hyperuricemia. Secondary to the lipid abnormalities, there is an increased risk of pancreatitis. The dyslipidemia, together with elevated erythrocyte aggregation, predisposes these patients to atherosclerosis. Premature atherosclerosis has not yet been clearly documented except for rare cases. Impaired platelet aggregation and increased antioxidative defense to prevent lipid peroxidation may function as a protective mechanism to help reduce the risk of atherosclerosis. Frequent fractures and radiographic evidence of osteopenia are common; bone mineral content is reduced even in prepubertal patients.

By the 2nd or 3rd decade of life, most patients with type I GSD exhibit hepatic adenomas that can hemorrhage and, in some cases, become malignant. Pulmonary hypertension has been seen in some long-term survivors of the disease. Iron refractory anemia and an increased prevalence of thyroid autoimmunity are also being recognized.

Renal disease is another complication, and most patients with type I GSD who are older than 20 yr of age have proteinuria. Many also have hypertension, renal stones, nephrocalcinosis, and altered creatinine clearance. Glomerular hyperfiltration, increased renal plasma flow, and microalbuminuria are often found in the early stages of renal dysfunction and can occur before the onset of proteinuria. In younger patients, hyperfiltration and hyperperfusion may be the only signs of renal abnormalities. With the advancement of renal disease, focal segmental glomerulosclerosis and interstitial fibrosis become evident. In some patients, renal function has deteriorated and progressed to failure, requiring dialysis and transplantation. Other renal...
abnormalities include amyloidosis, a Fanconi-like syndrome, hypocitraturia, hypercalciuria, and a distal renal tubular acidification defect.

**Diagnosis**

The diagnosis of type I GSD is suspected on the basis of clinical presentation and the laboratory findings of hypoglycemia, lactic acidosis, hyperuricemia, and hyperlipidemia. Neutropenia is noted in GSD Ib patients, typically before 1 yr of age. It has also been noted in some cases of GSD la, especially those with the mutation p.G188A. Administration of glucagon or epinephrine results in little or no rise in blood glucose level, but the lactate level rises significantly. Before the glucose-6-phosphatase and glucose-6-phosphate translocase genes were cloned, a definitive diagnosis required a liver biopsy. Gene-based mutation analysis provides a noninvasive way to diagnose most patients with types la and Ib disease.

**Treatment**

Treatment is designed to maintain normal blood glucose levels and is achieved by continuous nasogastric infusion of glucose or oral administration of uncooked cornstarch. Nasogastric drip feeding can be introduced in early infancy from the time of diagnosis. It can consist of an elemental formula or contain only glucose or a glucose polymer to provide sufficient glucose to maintain euglycemia during the night. Frequent feedings with high-carbohydrate content are given during the day.

Uncooked cornstarch acts as a slow-release form of glucose and can be introduced at a dose of 1.6 g/kg every 4 hr for children younger than 2 yr of age. The response of young children is variable. As the child grows older, the cornstarch regimen can be changed to every 6 hr at a dose of 1.6–2.5 g/kg of body weight. New starch products, which are currently being developed, are thought to be longer acting, better tolerated, and more palatable. A short-term double-blind crossover pilot study comparing uncooked, physically modified cornstarch to traditional cornstarch showed that the majority of GSD I patients treated with the new starch had better short-term metabolic control and longer duration of euglycemia, especially at night. However, more extensive studies replicating these results are necessary. Because fructose and galactose cannot be converted directly to glucose in GSD type I, these sugars are restricted in the diet. Sucrose (table sugar, cane sugar, other ingredients), fructose (fruit, juice, high fructose corn syrup), lactose (dairy foods), and sorbitol should be avoided or limited. As a result of these dietary restrictions, vitamins and minerals such as calcium and vitamin D may be deficient and supplementation is required to prevent nutritional deficiencies. Dietary therapy improves hyperuricemia, hyperlipidemia, and renal function, slowing the development of renal failure. This therapy fails, however, to normalize blood uric acid and lipid levels completely in some individuals, despite good metabolic control, especially after puberty. The control of hyperuricemia can be further augmented by the use of allopurinol, a xanthine oxidase inhibitor. The hyperlipidemia can be reduced with lipiodowering drugs such as beta-hydroxy-beta-methylglutaryl-Coenzyme A (HMG-CoA) reductase inhibitors and fibrates (see Chapter 86). Microalbuminuria, an early indicator of renal dysfunction in type I disease, is treated with angiotensin-converting enzyme inhibitors. Citrate supplements can be beneficial for patients with hypocitraturia by preventing or ameliorating nephrocalcinosis and development of urinary calculi. Growth hormone should be used with extreme caution and limited to only those with a documented growth hormone deficiency. Even in those cases, there should be close monitoring of metabolic parameters and presence of adenomas.

In patients with type Ib GSD, granulocyte and granulocyte-macrophage colony-stimulating factors are successful in correcting the neutropenia, decreasing the number and severity of bacterial infections, and improving the chronic inflammatory bowel disease. The minimum effective dose should be used, as side effects are noted on these agents, including splenomegaly, hypersplenism, and bone pain.

Orthotopic liver transplantation is a potential cure of type I GSD. However, the inherent short- and long-term complications leave this as a treatment of last resort, usually for patients with liver malignancy, multiple liver adenomas, metabolic derangements refractory to medical management, and/or liver failure. Large adenomas (>2 cm) that are rapidly increasing in size and/or number may require partial hepatic resection. Smaller adenomas (<2 cm) can be treated with percutaneous ethanol injection or transcatheter arterial embolization. A challenge is the recurrence of liver adenomas with potential for malignant transformation in these patients, ultimately requiring a liver transplant.

Bone marrow transplantation has been reported to correct the neutropenia of type Ib GSD.

Before any surgical procedure, the bleeding status must be evaluated and good metabolic control established. Prolonged bleeding times can be normalized by the use of intensive intravenous glucose infusion for 24–48 hr before surgery. Use of 1-deamino-8-arginine vasopressin (DDAVP) can reduce bleeding complications. Lactated Ringer solution should be avoided because it contains lactate and no glucose. Glucose levels should be maintained in the normal range throughout surgery with the use of 10% dextrose. Overall, metabolic control is assessed by growth, improvement, and correction of the metabolic abnormalities such as elevated lactate, glucose, triglyceride, cholesterol, and uric acid levels.

**Prognosis**

Previously, many patients with type I GSD died at a young age, and the prognosis was guarded for those who survived. Long-term complications occur mostly in adults whose disease was not adequately treated during childhood. Early diagnosis and effective treatment have improved the outcome, although renal disease and formation of hepatic adenomas with potential risk for malignant transformation remain serious complications. The ability to identify transformation to hepatocellular carcinoma in the liver adenomas remains a challenge: α-fetoprotein and carcinoembryonic antigen levels often remain normal in the setting of hepatocellular carcinoma.

**Type III Glycogen Storage Disease (Debrancher Deficiency, Limit Dextrinosis)**

Type III GSD is caused by a deficiency of glycogen debranching enzyme activity. Debranching enzyme, together with phosphorylase, is responsible for complete degradation of glycogen. When debranching enzyme is defective, glycogen breakdown is incomplete and an abnormal glycogen with short outer branch chains and resembling limit dextrin accumulates. Deficiency of glycogen debranching enzyme causes hepatomegaly, hypoglycemia, short stature, variable skeletal myopathy, and variable cardiomyopathy. The disorder usually involves both liver and muscle and is termed type IIIa GSD. In approximately 15% of patients, the disease appears to involve only liver and is classified as type IIIb.

Type III glycogenosis is an autosomal recessive disease that has been reported in many different ethnic groups; the frequency is relatively high in Sephardic Jews from North Africa. The gene for debranching enzyme is located on chromosome 1p21. More than 40 different mutations are identified; 2 exon 3 mutations c.18_19delGA (previously described as c.17_18delAG) and p.Gln6X are specifically associated with glycogenosis IIIb. Carrier detection and prenatal diagnosis are possible using DNA-based linkage or mutation analysis.

**Clinical Manifestations**

During infancy and childhood, the disease may be indistinguishable from type I GSD, because hepatomegaly, hypoglycemia, hyperlipidemia, and growth retardation are common (Fig. 87-2). Splenomegaly may be present, but the kidneys are not enlarged. Hepatomegaly and hepatic symptoms in most patients with type III GSD improve with age; however, progressive liver cirrhosis and failure can occur. Hepatocellular carcinoma has also been reported, more typically in patients with progressive liver cirrhosis. The frequency of adenomas in individuals with GSD III is far less than in individuals with GSD I. Furthermore, the relationship of hepatic adenomas and malignancy in GSD III is unclear. α-Fetoprotein and carcinoembryonic antigen levels are not good predictors of the presence of hepatocellular adenomas or malignant transformation. A single case of malignant transformation
Growth and development in a patient with type IIIb adult polyglucosan body disease. For adult life, glucagon may provoke no change in blood glucose level. After an overnight meal provokes a normal increase in blood glucose; after an overnight fast, glucagon may provoke no change in blood glucose level. The fibrosis and the paucity of fat distinguish type III glycogenosis from type I. The fibrosis, which ranges from minimal periportal fibrosis to micronodular cirrhosis, appears in most cases to be nonprogressive. Overt cirrhosis has been seen in some patients with GSD III.

Patients with myopathy and liver symptoms have a generalized enzyme defect (type IIIa). The deficient enzyme activity can be demonstrated not only in liver and muscle, but also in other tissues such as heart, erythrocytes, and cultured fibroblasts. Patients with hepatic symptoms without clinical or laboratory evidence of myopathy have debranching enzyme deficiency only in the liver, with enzyme activity retained in the muscle (type IIIb). Definite diagnosis requires enzyme assay in liver, muscle, or both. Mutation analysis can provide a noninvasive method for diagnosis and subtype assignment in the majority of patients.

**Treatment**

Dietary management is less demanding than in type I GSD. Patients do not need to restrict dietary intake of fructose and galactose. If hypoglycemia is present, frequent meals high in carbohydrates with cornstarch supplements or nocturnal gastric drip feedings are usually effective. A high-protein diet during the daytime plus overnight protein enteral infusion is also effective in preventing hypoglycemia and preventing endogenous protein breakdown because protein can be used as a substrate for gluconeogenesis, a pathway that is intact in type III GSD. There is no satisfactory treatment for the progressive myopathy other than recommending a high-protein diet and an exercise program. Liver transplantation has been performed in GSD III patients with progressive cirrhosis and/or hepatic carcinoma. There are reports of cardiac transplant in GSD III patients with end stage cardiac disease.

**Type IV Glycogen Storage Disease (Branching Enzyme Deficiency, Amylopectinosis, or Andersen Disease)**

Deficiency of branching enzyme activity results in accumulation of an abnormal glycogen with poor solubility. The disease is referred to as type IV GSD or amylopectinosis because the abnormal glycogen has fewer branch points, more α-1-4 linked glucose units, and longer outer chains, resulting in a structure resembling amylopectin. Type IV GSD is an autosomal recessive disorder. The glycogen branching enzyme (GBE) gene is located on chromosome 3p21. More than 20 mutations responsible for type IV GSD have been identified, and their characterization in individual patients can be useful in predicting the clinical outcome. The nearly complete absence of GBE activity with null mutations has been associated with perinatal death and fatal neonatal hypotonia. Residual GBE enzyme activity of greater than 5% and at least 1% missense mutation are associated with a nonlethal phenotype and, in some situations, a lack of progressive liver disease.

**Clinical Manifestations**

This disorder is clinically variable. The most common and classic form is characterized by progressive cirrhosis of the liver and is manifested in the first 18 mo of life as hepatosplenomegaly and failure to thrive. The cirrhosis progresses to portal hypertension, ascites, esophageal varices, and liver failure that usually lead to death by 5 yr of age. Rare patients survive without progression of liver disease; these patients have a milder hepatic form and do not require a liver transplant.

A neuromuscular form of the disease has been reported with 4 main variants recognized based on age of presentation. The perinatal form presents as a fetal akinesia deformation sequence and death in the perinatal period. The congenital form presents at birth with severe hypotonia, muscle atrophy, and neuronal involvement with death in the neonatal period; some patients have cardiomyopathy. The childhood form presents primarily with myopathy or cardiomyopathy. The adult form presents with diffuse central and peripheral nervous system dysfunction accompanied by accumulation of polyglucosan material in the nervous system (adult polyglucosan body disease). For adult polyglucosan disease, a leukocyte or nerve biopsy is needed to establish the diagnosis as branching enzyme deficiency is limited to those tissues.
Diagnosis

Tissue deposition of amylopectin-like materials can be demonstrated in liver, heart, muscle, skin, intestine, brain, spinal cord, and peripheral nerve. The hepatic histologic findings are characterized by micronodular cirrhosis and faintly stained basophilic inclusions in the hepatocytes. The inclusions consist of coarsely clumped, stored material that is periodic acid–Schiff positive and partially resistant to diastase digestion. Electron microscopy shows, in addition to the conventional α and β glycogen particles, accumulation of the fibrillar aggregations that are typical of amylopectin. The distinct staining properties of the cytoplasmic inclusions, as well as electron microscopic findings, could be diagnostic. However, polysaccharides with histologic features reminiscent of type IV disease, but without enzymatic correlation, have been observed. The definitive diagnosis rests on the demonstration of the deficient branching enzyme activity in liver, muscle, cultured skin fibroblasts, or leukocytes, or on the identification of disease-causing mutations in the GBE gene. Prenatal diagnosis is possible by measuring the enzyme activity in cultured amniocytes, chorionic villi, or mutation analysis.

Treatment

There is no specific treatment for type IV GSD. Unlike patients with the other liver GSDs (I, III, VI, IX), those with GSD IV do not have hypoglycemia, which is only seen when there is overt liver cirrhosis. Liver transplantation has been performed for patients with progressive hepatic failure, but because it is a multisystem disorder involving many organ systems, the long-term success of liver transplantation is unknown. Individuals with significant diffuse reticuloendothelial involvement may have greater risk for morbidity and mortality, which may impact the success rate for liver transplants. Caution should be taken in selecting type IV patients for liver transplantation because these patients have variable phenotypes, which include a nonprogressive form of the liver disease and in some cases, extrahepatic manifestations of the disease.

Type VI Glycogen Storage Disease (Liver Phosphorylase Deficiency, Hers Disease)

There are few patients with documented liver phosphorylase deficiency. Such patients usually have a benign course and present with hepatomegaly and growth retardation in early childhood; however, some cases are more severe. Hypoglycemia, hyperlipidemia, and hyperketosis are of variable severity. Lactic acid and uric acid levels are normal. The heart and skeletal muscles are not involved. The hepatomegaly and growth retardation improve with age and usually disappear around puberty. Some patients with severe hepatomegaly, recurrent severe hypoglycemia, hyperketosis, and postprandial lactic acidosis have recently been reported. Treatment is symptomatic, as some patients require no specific treatment. A high-carbohydrate, high-protein diet and frequent feeding are effective in preventing hypoglycemia. Blood glucose and ketones should be monitored routinely, especially during periods of increased activity/illness.

GSD VI is an autosomal recessive disease. Diagnosis can be confirmed through molecular testing of the liver phosphorylase gene (PYGL), which is found on chromosome 14q21-22 and has 20 exons. Many mutations are known in this gene; a splice-site mutation in intron 13 has been identified in the Mennonite population. A liver biopsy showing elevated glycogen content and decreased hepatic phosphorylase enzyme activity can also be used to make a diagnosis.

Type IX Glycogen Storage Disease (Phosphorylase Kinase Deficiency)

This disorder represents a heterogeneous group of glycogenoses. Phosphorylase, the rate-limiting enzyme of glycogenolysis, is activated by a cascade of enzymatic reactions involving adenylate cyclase, cyclic adenosine monophosphate–dependent protein kinase (protein kinase A), and phosphorylase kinase. The latter enzyme has 4 subunits (α, β, γ, δ), each encoded by different genes on different chromosomes and differentially expressed in various tissues. This cascade of reactions is stimulated primarily by glucagon. Glycogenosis could be the result of any enzyme deficiency along this pathway; the most common is the deficiency of phosphorylase kinase. Phosphorylase kinase (PhK) deficiency varies clinically as a result of defects in the various genes encoding the four subunits of the protein. In the PHKA1 gene causes muscle PhK deficiency; mutations in the PHKA2 and PHKG2 genes cause liver PhK deficiency; mutations in the PHKB gene cause PhK deficiency in liver and muscle. Mutations in the PHKG1 gene have not been identified. Defects in subunits α, β, γ, and δ are responsible for liver phosphorylase kinase deficiency. Liver PhK deficiency’s physical features are usually recognizable within the first 2 yr of life and include short stature and abdominal distention from moderate to marked hepatomegaly. The clinical severity of liver PhK deficiency varies considerably. Hyperketotic hypoglycemia, if present, is usually mild but can be severe in some cases. Ketosis may occur even when glucose levels are normal. In some children, there may be mild delays in gross motor development and hypotonia. Liver fibrosis can occur and progress to cirrhosis in rare cases, particularly in patients with PHKG2 mutations. Liver adenoma appears to be very rare. Cognitive and speech delays have been reported in a few individuals, but it is not clear whether these delays are caused by PhK deficiency or whether they are coincidental. Polycystic ovaries are common in females with liver PhK deficiency. Renal tubular acidosis has been reported in rare cases. Cardiac manifestations have not been reported. Unlike in GSD I, lactic acidosis, bleeding tendency, and loose bowel movements are not characteristic. Although growth is retarded during childhood, normal height and complete sexual development are eventually achieved. As with debrancher deficiency, abdominal distention and hepatomegaly usually decrease with age and may disappear by adolescence. Most adults with liver PhK deficiency are asymptomatic, although further long-term studies are needed to fully assess the impact of this disorder in adults. Phenotypic variability within each subtype is being uncovered with the availability of molecular testing. The incidence of all subtypes of PhK deficiency is approximately 1:100,000 live births.

X-Linked Liver Phosphorylase Kinase Deficiency

X-linked liver PhK deficiency is the most common form of liver glycogenoses. In addition to liver, enzyme activity can also be deficient in erythrocytes, leukocytes, and fibroblasts; it is normal in muscle. Typically, a 1-5 yr old male presents with growth retardation, an incidental finding of hepatomegaly, and a slight delay in motor development. Cholesterol, triglycerides, and liver enzymes are mildly elevated. Ketosis may occur after fasting. Lactate and uric acid levels are normal. Hypoglycemia is typically mild, if present, but can be severe. The response in blood glucose to glucagon is normal. Hepatomegaly and abnormal blood chemistries gradually improve and can normalize with age. Most adults achieve a normal final height and are usually asymptomatic despite a persistent PhK deficiency. In rare cases, liver fibrosis can occur and progress to cirrhosis. Liver histology shows glycogen-distended hepatocytes, steatosis, and potentially mild portal fibrosis. The accumulated glycogen (β particles, rosette form) has a frayed or burst appearance and is less compact than the glycogen seen in type I or type III GSD. Fibrous septal formation and low-grade inflammatory changes may be present.

The structural gene for the common liver isoform of the PhK α subunit, PHKA2, is located on the X chromosome (α1 at Xp22.2). Mutations in the PHKA2 gene account for 75% of all PhK cases. X-linked liver PhK deficiency is further subdivided into 2 biochemical subtypes: XLG1, with measurable deficiency of PhK activity in both blood cells and liver, and XLG2, with normal in vitro PhK activity in blood cells and variable activity in liver. It is suspected that XLG2 may be caused by missense mutations that affect enzyme regulation, while nonsense mutations affecting the amount of protein result in XLG1.

Autosomal Liver and Muscle Phosphorylase Kinase Deficiency

PhK deficiency in liver and blood cells with an autosomal mode of inheritance has been reported. As with the X-linked form, hepatomegaly and growth retardation are the predominant symptoms in early
childhood. Some patients also exhibit muscle hypotonia. In a few cases where enzyme activity has been measured, reduced PhK activity has been demonstrated in muscle. Mutations causing milder autosomal transmitted liver and muscle PhK deficiency are found in the PHKB gene (chromosome 16q12-q13), which encodes the β subunit. Several nonsense mutations, a single-base insertion, a splice-site mutation, and a large intragenic mutation have been identified. In addition, a mis-sense mutation was discovered in an atypical patient with normal blood cell PhK activity.

**Autosomal Liver Phosphorylase Kinase Deficiency**

This form of PhK deficiency is caused by mutations in the testis/liver isoform of the γ subunit gene (TL, PHKG2). In contrast to X-linked PhK deficiency, patients with mutations in the PHKG2 gene typically have more severe phenotypes with recurrent hypoglycemia and often develop progressive liver cirrhosis. PHKG2 maps to chromosome 16p12.1-p11.2; many disease-causing mutations are known for this gene.

**Muscle-Specific Phosphorylase Kinase Deficiency**

A few cases of PhK deficiency restricted to muscle are known. Patients, both male and female, present either with muscle cramps and myoglobinuria with exercise or with progressive muscle weakness and atrophy. PhK activity is decreased in muscle but normal in liver and blood cells. There is no hepatomegaly or cardiomegaly. The structural gene for the muscle-specific form α subunit (αM) is located at Xq12. Mutations of the gene have been found in some male patients with this disorder. The gene for muscle γ subunit (γM, PHKG1) is on chromosome 7p12. No mutations in this gene have been reported so far.

**Phosphorylase Kinase Deficiency Limited to Heart**

These patients present with cardiomyopathy in infancy and rapidly progress to heart failure and death. PhK deficiency is demonstrated in the heart with normal enzyme activity in skeletal muscle and liver. Studies have questioned the existence of cardiac-specific primary PhK deficiency. However, the disease presentation has now been linked to the γ2 subunit of adenosine monophosphate–activated protein kinase (see “Glycogen Storage Diseases Mimicking Hypertrophic Cardiomyopathy” below). The γ2 subunit is encoded by the PRKAG2 gene.

**Diagnosis**

Definitive diagnosis of PhK deficiency requires demonstration of the enzymatic defect in affected tissues. PhK can be measured in leukocytes and erythrocytes, but because the enzyme has many isozymes, the diagnosis can be easily missed without studies of liver, muscle, or heart. Mutation analysis is necessary in many cases to determine the disease’s subtype. Individuals with liver PhK deficiency also usually have elevated transaminases, mildly elevated triglycerides and cholesterol, normal uric acid and lactate acid concentrations, and normal glucagon responses.

The PHKA2 gene encoding the α subunit is most commonly involved, followed by the PHKB gene encoding the β subunit, regardless of the presence of deficiency in erythrocytes. Mutations in the PHKG2 gene underlying γ-subunit deficiency are typically associated with severe liver involvement with recurrent hypoglycemia and liver fibrosis.

**Treatment**

The treatment for liver PhK deficiency is symptomatic. It includes a high-carbohydrate, high-protein diet and frequent feedings to prevent hypoglycemia, although many patients require no specific treatment. Cornstarch can be administered with symptom-dependent dosage and timing (0.6-2.3 g/kg every 6 hr). Oral intake of glucose, if tolerated, should be used to treat hypoglycemia. If not, intravenous glucose should be given. Prognosis for the X-linked and certain autosomal forms is typically good, however, patients with mutations in the γ subunit typically have a more severe clinical course with progressive liver disease. There is no treatment for the fatal form of isolated cardiac PhK deficiency other than heart transplantation.

**Glycogen Synthase Deficiency**

Deficiency of hepatic glycogen synthase (GYS2) activity leads to a marked decrease of glycogen stored in the liver. The gene for GYS2 is located at 12p12.2. Several mutations of this gene have been identified in patients with GSD 0. The disease appears to be rare in humans, and in the true sense, this is not a type of GSD because the deficiency of the enzyme leads to decreased glycogen stores. Patients present in infancy with early morning (prebreakfast) drowsiness, pallor, emesis, and fatigue, and sometimes convulsions associated with hypoglycemia and hyperketonemia. Blood lactate and alanine levels are low, and there is no hyperlipidemia or hepatomegaly. Prolonged hyperglycemia, hyperuricemia, and elevation of lactate with normal insulin levels after administration of glucose or a meal suggest a possible diagnosis of deficiency of glycogen synthase. Definitive diagnosis requires a liver biopsy to measure the enzyme activity or identification of mutations in the liver glycogen synthase gene, located on chromosome 12p12.2. Treatment consists of frequent meals, rich in protein, and nighttime supplementation with uncooked cornstarch to prevent hypoglycemia and hyperketonemia. Most children with GSD 0 are cognitively and developmentally normal. Short stature and osteopenia are common features. The prognosis seems good for patients who survive to adulthood, including resolution of hypoglycemia, except during pregnancy.

**Muscle Glycogen Synthase Deficiency**

This GSD results from muscle glycogen synthase (glycogen synthase 1, GYS1) deficiency. The gene for GYS1 has been localized to chromosome 19q13.3. The disease is extremely rare and was reported in 3 children of consanguineous parents of Syrian origin. Muscle biopsies showed lack of glycogen, predominantly oxidative fibers, and mitochondrial proliferation. Glucose tolerance was normal. Molecular study revealed a homozygous stop mutation (R462→ter) in the muscle glycogen synthase gene. The phenotype was variable in the 3 siblings and ranged from sudden cardiac arrest, muscle fatigability, hypertrophic cardiomyopathy, an abnormal heart rate, and hypotension while exercising, to mildly impaired cardiac function at rest.

**Hepatic Glycogenosis with Renal Fanconi Syndrome (Fanconi-Bickel Syndrome)**

This rare autosomal recessive disorder is caused by defects in the facilitative glucose transporter 2 (GLUT-2), which transports glucose in and out of hepatocytes, pancreatic β cells, and the basolateral membranes of intestinal and renal epithelial cells. The disease is characterized by proximal renal tubular dysfunction, impaired glucose and galactose utilization, and accumulation of glycogen in liver and kidney. The affected child typically presents in the first year of life with failure to thrive, rickets, and a protuberant abdomen from hepato-megal and nephromegaly. The disease may be confused with GSD type I because a Fanconi-like syndrome can also develop in type I disease patients. Adults commonly present with short stature, dwarfism, and excess fat in the abdomen and shoulders. Patients are more susceptible to fractures owing to early-onset generalized osteopenia. In addition, intestinal malabsorption and diarrhea may occur.

Laboratory findings include glucosuria, phosphaturia, generalized aminoaciduria, bicarbonate wasting, hypophosphatemia, increased serum alkaline phosphatase levels, and radiologic findings of rickets. Mild fasting hypoglycemia and hyperlipidemia may be present. Liver transaminase, plasma lactate, and uric acid levels are usually normal. Oral galactose or glucose tolerance tests show intolerance, which could be explained by the functional loss of GLUT-2 preventing liver uptake of these sugars. Tissue biopsy results show marked accumulation of glycogen in hepatocytes and proximal renal tubular cells, presumably owing to the altered glucose transport out of these organs. Diffuse glomerular mesangial expansion along with glomerular hyperfiltration and microalbuminuria similar to nephropathy in GSD Ia and diabetes have been reported.
Fanconi-Bickel syndrome is rare. Seventy percent of patients with a detectable GLUT-2 mutation have consanguineous parents. Most patients are homozygous for the disease-related mutations; some patients are compound heterozygotes. The majority of mutations detected thus far predict a premature termination of translation. The resulting loss of the C-terminal end of the GLUT-2 protein predicts a nonfunctioning glucose transporter with an inward-facing substrate-binding site.

There is no specific treatment. Symptom-dependent treatment with phosphate and bicarbonate can result in growth improvement. Symptomatic replacement of water, electrolytes, and vitamin D; restriction of galactose intake; and a diet similar to that used for diabetes mellitus presented in frequent and small meals with an adequate caloric intake may also improve growth.

**MUSCLE GLYCOGENOSES**

The role of glycogen in muscle is to provide substrates for the generation of ATP for muscle contraction. The muscle GSDs are broadly divided into 2 groups. The first group is characterized by hypertrophic cardiomyopathy, progressive skeletal muscle weakness and atrophy, or both, and includes deficiencies of acid α-glucosidase, a lysosomal glycolysis degrading enzyme (type II GSD), lysosomal-associated membrane protein 2 (LAMP2), and adenosine monophosphate–activated protein kinase γ2 (PRKAG2). The second group comprises muscle energy disorders characterized by muscle pain, exercise intolerance, myoglobinuria, and susceptibility to fatigue. This group includes myophosphorylase deficiency (McArdle disease, type V) and deficiencies of phosphofructokinase (type VII), phosphoglycerate kinase, phosphoglycerate mutase, and lactate dehydrogenase. Some of these latter enzyme deficiencies can also be associated with compensated hemolytic anemia, suggesting a more generalized defect in glucose metabolism.

**Type II Glycogen Storage Disease (Lysosomal Acid α-1,4-Glucosidase Deficiency, Pompe Disease)**

Pompe disease, also referred to as GSD type II or acid maltase deficiency, is caused by a deficiency of acid α-1,4-glucosidase (acid maltase), an enzyme responsible for the degradation of glycogen in lysosomes. This enzyme defect results in lysosomal glycogen accumulation in multiple tissues and cell types, with cardiac, skeletal, and smooth muscle cells being the most seriously affected. The disease is characterized by accumulation of glycogen in lysosomes, as opposed to its accumulation in cytoplasm in the other glycogenoses. Pompe disease is an autosomal recessive disorder with an incidence of approximately 1 in 40,000 live births in whites and 1 in 18,000 live births in Han Chinese. The gene for acid α-glucosidase is on chromosome 17q25.2. Multiple pathogenic mutations have been identified that could be helpful in delineating the phenotypes. An example is a splice-site mutation (IVS1-13T→G; c.-32-13T>G), commonly seen in late-onset patients of white race.

**Clinical Manifestations**

The disorder encompasses a range of phenotypes, each including myopathic but differing in age at onset, organ involvement, and clinical severity. **Infantile Pompe disease** was uniformly lethal without enzyme replacement therapy with alglucosidase alfa. Affected infants present in the first few weeks to months of life with hypotonia, a generalized muscle weakness with a “floppy infant” appearance, neuromuscular bulbar weakness, feeding difficulties, macroglosis, hepatomegaly, and a hypertrophic cardiomyopathy followed by death from cardiorespiratory failure or respiratory infection usually by 1 yr of age.

**Late-onset Pompe disease (juvenile and adult-onset disease)** is characterized by a lack or absence of severe cardiac involvement and a less-severe short-term prognosis. Symptoms related to progressive dysfunction of skeletal muscles can start as early as 1 yr of age to as late as the 6th decade of life. The clinical picture is dominated by slowly progressive proximal muscle weakness with truncal involvement and greater involvement of the lower limbs than the upper limbs. The pelvic girdle, paraspinal muscles, and diaphragm are the muscle groups most seriously affected. Other symptoms may include lingual weakness, ptosis, and dilation of blood vessels such as the basilar artery and the ascending aorta. These patients often present with proximal or limb girdle muscle weakness. With disease progression, patients become confined to wheelchairs and require artificial ventilation. The initial symptoms in some patients may be respiratory insufficiency manifested by somnolence, morning headache, orthopnea, and exertional dyspnea, which eventually lead to sleep-disordered breathing and respiratory failure. Respiratory failure is the cause of significant morbidity and mortality in this form of the disease. Basilar artery aneurysms with rupture also contribute to mortality in some cases. The age of death varies from early childhood to late adulthood, depending on the rate of disease progression and the extent of respiratory muscle involvement. With the advent of enzyme replacement therapy, a new picture of the natural history is emerging for both infantile and late onset patients with Pompe disease.

**Laboratory Findings**

These include elevated levels of serum creatine kinase, aspartate aminotransferase, and lactate dehydrogenase. In the infantile form a chest x-ray showing massive cardiomegaly is frequently the first symptom detected. Electrocardiographic findings include a high-voltage QRS complex and a shortened PR interval. Echocardiography reveals thickening of both ventricles and/or the intraventricular septum and/or left ventricular outflow tract obstruction. Muscle biopsy shows the presence of vacuoles that stain positively for glycogen; acid phosphatase is increased, presumably from a compensatory increase of lysosomal enzymes. Electron microscopy reveals glycogen accumulation within the membranous sac and in the cytoplasm. Electromyography reveals myopathic features with excessive electrical irritability of muscle fibers and pseudomyotonic discharges. Serum creatine kinase is not always elevated in adult patients. Depending on the muscle sampled or tested, the muscle histologic appearance and electromyography may not be abnormal.

Some patients with infantile Pompe disease who had peripheral nerve biopsies demonstrated glycogen accumulation in the neurons and Schwann cells, too. Infantile Pompe disease may manifest both myopathic and neuropathic clinical signs. Generally, the former predominate.

**Diagnosis**

The confirmatory step for a diagnosis of Pompe disease is enzyme assay demonstrating deficient acid α-glucosidase or gene sequencing showing 2 pathogenic mutations in the GAA gene. The enzyme assay is usually done in dried blood spots, leukocytes, blood mononuclear cells, muscle, and cultured skin fibroblasts, using maltose, glycogen, or 4-methylumbelliferyl-α-d-glucopyranoside (4MUG) as a substrate. Deficiency is usually more severe in the infantile form than in the late-onset forms. The skin fibroblast assay is usually preferred to muscle biopsy because it is a less-invasive procedure with the advantage of maintaining a cell line for future use and providing information on residual enzyme activity. Blood-based assays, especially dried blood spots, have the advantage of a rapid turnaround time. A muscle biopsy can yield faster results and provide additional information about glycogen content and site of glycogen storage within and outside the lysosomes of muscle cells. A major limitation of a muscle biopsy in late-onset patients is the variable pathology and glycogen accumulation in different muscles and within muscle fibers; muscle histology and glycogen content can vary depending on the site of muscle biopsy. There is also a high risk from anesthesia in infantile patients. An electrocardiogram can be helpful in making the diagnosis in suspected cases of the infantile form and should be done for patients suspected of having Pompe disease before any procedure requiring anesthesia, including muscle biopsy, is performed. Urinary glucose tetrasaccharides are elevated in the urine of affected patients, and levels are extremely high in infantile patients. This biomarker is valuable for diagnosis and monitoring response to therapy in Pompe disease. Prenatal diagnosis using amniocytes or chorionic villi is available for the infantile form of the disease.
Part XI ◆ Metabolic Disorders

Metabolic Disorders present in early infancy with severe hypertrophic cardiomyopathy and a rapidly fatal course. In the past, several of these cases were misdiagnosed as GSD IX as a result of secondary low PhK activity in the heart. The p.Arg531Gln and p.Arg384Thr mutations in the PRKAG2 gene are incompatible with life. Other mutations (p.Arg302Gln, p.Thr400An, p.Asn488Ile, and p.His487Tyr) associated with Wolff-Parkinson-White syndrome and adult-onset hypertrophic cardiomyopathy are less disruptive.

The prognosis for LAMP2 deficiency is poor with progressive end-stage heart failure early in adulthood. With the exception of the fatal infantile presentation, cardiomyopathy caused by PRKAG2 mutations is compatible with long-term survival, although some patients may necessitate the implantation of a pacemaker and aggressive control of arrhythmias.

Type V Glycogen Storage Disease (Muscle Phosphorylase Deficiency, McArdle Disease)

GSD V is caused by the deficiency of muscle phosphorylase activity. Lack of this enzyme limits muscle ATP generation by glycogenolysis, resulting in muscle glycogen accumulation, and is the prototype of muscle energy disorders. A deficiency of myophosphorylase impairs the cleavage of glucosyl molecules from the straight chain of glycogen.

Clinical Manifestations

Symptoms usually first develop in late childhood or in the 2nd decade of life. In general, clinical heterogeneity is uncommon, but cases suggesting otherwise have been documented. Studies have shown that McArdle disease can manifest in individuals as old as 74 yr of age, as well as in infancy, in a fatal, early-onset form characterized by hypotonia, generalized muscle weakness, and respiratory complication. Symptoms are generally characterized by exercise intolerance with muscle cramps and pain. Two types of activity tend to cause symptoms: brief exercise of great intensity, such as sprinting or carrying heavy loads; and less intense but sustained activity, such as climbing stairs or walking uphill. Moderate exercise, such as walking on level ground,
can be performed by most patients for long periods. Many patients experience a characteristic "second wind" phenomenon. If they slow down or pause briefly at the first appearance of muscle pain, they can resume exercise with more ease. As a result of the underlying myopathy, these patients may be at risk for statin-induced myopathy and rhabdomyolysis. While patients typically experience episodic muscle pain and cramping from exercise, 35% of patients with McArdle disease report permanent pain that has a serious impact on sleep and other activities. Studies also suggest that there may also be a link between GSD V and levels of cognitive impairment.

Approximately 50% of patients report burgundy-colored urine after exercise, which is the consequence of exercise-induced myoglobinuria secondary to rhabdomyolysis. Intense myoglobinuria after vigorous exercise may cause acute renal failure. In rare cases, electromyographic findings may suggest an inflammatory myopathy and the diagnosis can be confused with polymyositis.

The level of serum creatine kinase is usually elevated at rest and increases more after exercise. Exercise also increases the levels of blood ammonia, inosine, hypoxanthine, and uric acid. The latter abnormalities are attributed to accelerated recycling of muscle purine nucleotides owing to insufficient ATP production. Type V GSD is an autosomal recessive disorder. The gene for muscle phosphorylase (PYGM) has been mapped to chromosome 11q13.

Diagnosis
The standard diagnosis for GSD V includes a muscle biopsy to measure glycogen content as well as enzyme and mutation analysis. An ischemic exercise test offers a rapid diagnostic screening for patients with a metabolic myopathy. Lack of an increase in blood lactate levels and exaggerated blood ammonia elevations indicate muscle glycogenosis and suggest a defect in the conversion of muscle glycogen or glucose to lactate. The abnormal ischemic exercise response is not limited to type V GSD. Other muscle defects in glycogenolysis or glycolysis produce similar results (deficiencies of muscle phosphofructokinase, phosphoglycerate kinase, phosphoglycerate mutase, and lactate dehydrogenase).

Phosphorus MRI allows for the noninvasive evaluation of muscle metabolism. Patients with type V GSD have no decrease in intracellular pH and have excessive reduction in phosphocreatine in response to exercise. The diagnosis should be confirmed by enzymatic evaluation of muscle. A common nonsense mutation p.R49X in exon 1 is found in 90% of white patients, and a deletion of a single codon in exon 17 is found in 61% of Japanese patients. The p.R49X mutation represents 55% of alleles in Spanish patients, whereas the p.W797R mutation represents 14% and the p.G204S represents 9% of mutant alleles in the Spanish population. There seems to be an association between clinical severity of GSD V and the presence of the D allele of the angiotensin-converting enzyme insertion/deletion polymorphism. This may help explain the spectrum of phenotypic variability manifested in this disorder.

Treatment
Avoidance of strenuous exercise prevents the symptoms; however, regular and moderate exercise is recommended to improve exercise capacity. Glucose or sucrose given before exercise or injection of glucagon can markedly improve tolerance in these patients. A high-protein diet may increase muscle endurance and creatine supplement has been shown to improve muscle function in some patients. The clinical response to creatine is dose-dependent: muscle pain may increase on high doses of creatine supplementation. Vitamin B6 supplementation reduces exercise intolerance and muscle cramps. Longevity is not generally affected.

Type VII Glycogen Storage Disease (Muscle Phosphofructokinase Deficiency, Tarui Disease)
Type VII GSD is caused by a deficiency of muscle phosphofructokinase, which catalyzes the ATP-dependent conversion of fructose-6-phosphate to fructose-1,6-diphosphate and is a key regulatory enzyme of glycolysis. Phosphofructokinase is composed of 3 isoenzyme subunits (M [muscle], L [liver], and P [platelet]) that are encoded by different genes and differentially expressed in tissues. Skeletal muscle contains only the M subunit, and red blood cells contain a hybrid of L and M forms. Type VII disease is caused by a defective M isoenzyme, which causes a complete enzyme defect in muscle and a partial defect in red blood cells.

Type VII GSD is an autosomal recessive disorder and is prevalent among Japanese people and Ashkenazi Jews. The gene for muscle phosphofructokinase is located on chromosome 12q13.3. A splicing defect and a nucleotide deletion in the muscle phosphofructokinase gene account for 95% of mutant alleles in Ashkenazi Jews. Diagnosis based on molecular testing is thus possible in this population.

Clinical Manifestations
Six features of type VII are distinctive: (1) Exercise intolerance, usually evident in childhood, is more severe than in type V disease and may be associated with nausea, vomiting, and severe muscle pain; vigorous exercise causes severe muscle cramps and myoglobinuria. (2) Compensated hemolysis occurs as evidenced by an increased level of serum bilirubin and an elevated reticulocyte count. (3) Hyperuricemia is common and exaggerated by muscle exercise to a greater degree than that observed in type V or III GSD. (4) An abnormal polycaccharide is present in muscle fibers; it is periodic acid–Schiff-positive but resistant to diastase digestion. (5) Exercise intolerance is particularly acute after meals that are rich in carbohydrates because glucose cannot be utilized in muscle and because glucose inhibits lipolysis, thereby depriving muscle of fatty acid and ketone substrates. In contrast, patients with type V disease can metabolize bloodborne glucose derived from either liver glycogenolysis or exogenous glucose; indeed, glucose infusion improves exercise tolerance in type V patients. (6) There is no spontaneous second-wind phenomenon because of the inability to metabolize blood glucose.

Other rare type VII variants occur. One variant presents in infancy with hypotonia and limb weakness and proceeds to a rapidly progressive myopathy that leads to death by 4 yr of age. There is a second variant that occurs in infancy and results in congenital myopathy and arthrogryposis with a fatal outcome. A third variant presents in infancy with hypotonia, mild developmental delay and seizures. An additional presentation is hereditary nonspherocytic hemolytic anemia. Although these patients do not experience muscle symptoms, it remains unclear whether these symptoms will develop later in life. One variant presents in adults and is characterized by a slowly progressive, fixed muscle weakness rather than cramps and myoglobinuria. It may also cause mitral valve thickening from glycogen buildup.

Diagnosis
To establish a diagnosis, a biochemical or histochemical demonstration of the enzymatic defect in the muscle is required. The absence of the M isoenzyme of phosphofructokinase can also be demonstrated in blood cells and fibroblasts.

Other Muscle Glycogenoses with Muscle Energy Impairment
Six additional defects in enzymes—phosphoglycerate kinase, phosphoglycerate mutase, lactate dehydrogenase, fructose-1,6-bisphosphate aldolase A, muscle pyruvate kinase, and β-enolase in the pathway of the terminal glycolysis—cause symptoms and signs of muscle energy
imperative similar to those of types V and VII GSD. The failure of blood lactate to increase in response to exercise is a useful diagnostic test and can be used to differentiate muscle glycogenoses from disorders of lipid metabolism, such as carnitine palmitoyl transferase II deficiency and very long chain acyl-CoA dehydrogenase deficiency, which also cause muscle cramps and myoglobinuria. Muscle glycogen levels can be normal in the disorders affecting terminalglyolysis and assaying the muscle enzyme activity is needed to make a definite diagnosis. There is no specific treatment. Avoidance of strenuous exercise prevents acute attacks of muscle cramps and myoglobinuria. Avoidance of drugs such as statins, and malignant hyperthermia precautions for patients undergoing anesthesia should be followed.

**Bibliography is available at Expert Consult.**

### 87.2 Defects in Galactose Metabolism

**Priya S. Kishnani and Yuan-Tsong Chen**

Milk and dairy products contain lactose, the major dietary source of galactose. The metabolism of galactose produces fuel for cellular metabolism through its conversion to glucose-1-phosphate (see Table 87-1). Galactose also plays an important role in the formation of galactosides, which include glycoproteins, glycolipids, and glycosaminoglycans. Galactosemia denotes the elevated level of galactose in the blood and is found in 3 distinct inborn errors of galactose metabolism in 1 of the following enzymes: galactose-1-phosphate uridyl transferase, galactokinase, and uridine diphosphate galactose-4-epimerase. The term galactosemia, although adequate for the deficiencies in any of these disorders, generally designates the transferase deficiency.

**GALACTOSE-1-PHOSPHATE URIDYL TRANSFERASE DEFICIENCY GALACTOSEMIA**

Two forms of the deficiency exist: infants with complete or near complete deficiency of the enzyme (classic galactosemia) and those with partial transferase deficiency. Classic galactosemia is a serious disease with onset of symptoms typically by the second half of the 1st wk of life. The incidence is predicted to be 1 in 60,000 live births. The newborn infant receives high amounts of lactose (up to 40% in breast milk and certain formulas), which consists of equal parts of glucose and galactose. Without the transferase enzyme, the infant is unable to metabolize galactose-1-phosphate, the accumulation of which results in injury to kidney, liver, and brain. This injury may begin prenatally in the affected fetus by transplacental galactose derived from the diet of the heterozygous mother or by endogenous production of galactose in the fetus.

**Clinical Manifestations**

The diagnosis of uridyl transferase deficiency should be considered in newborn or young infants with any of the following features: jaundice, hepatomegaly, vomiting, hypoglycemia, seizures, lethargy, irritability, feeding difficulties, poor weight gain or failure to regain birth weight, aminoaciduria, nuclear cataracts, vitreous hemorrhage, hepatic failure, liver cirrhosis, ascites, splenomegaly, or intellectual disability. Symptoms are milder and improve when milk is temporarily withdrawn and replaced by intravenous or lactose-free nutrition. Patients with galactosemia are at increased risk for *Escherichia coli* neonatal sepsis; the onset of sepsis often precedes the diagnosis of galactosemia. Pseudotumor cerebri can occur and cause a bulging fontanel. Death from liver and kidney failure and sepsis may follow within days. When the diagnosis is not made at birth, damage to the liver (cirrhosis) and brain (intellectual disability) becomes increasingly severe and irreversible.

**Partial transferase deficiency** is generally asymptomatic. It is more frequent than classic galactosemia and is diagnosed in newborn screening because of moderately elevated blood galactose and/or low transferase activity. Galactosemia should be considered for the newborn or young infant who is not thriving or who has any of the preceding findings. Light and electron microscopy of hepatic tissue reveals fatty infiltration, the formation of pseudoacini, and eventual macronodular cirrhosis. These changes are consistent with a metabolic disease but do not indicate the precise enzymatic defect.

**Diagnosis**

The preliminary diagnosis of galactosemia is made by demonstrating a reducing substance in several urine specimens collected while the patient is receiving human milk, cow's milk, or any other formula containing lactose. The reducing substance found in urine by Clinistix (glucose, galactose, and others) can be identified by chromatography or by an enzymatic test specific for galactose. Galactosuria is present, provided the last milk feed does not date back more than a few hours and the child is not vomiting excessively. Clinistix urine test results are usually negative because the test materials rely on the action of glucose oxidase, which is specific for glucose and is nonreactive with galactose. Owing to a proximal renal tubular syndrome, the acutely ill baby may also excrete glucose together with amino acids. Because galactose is injurious to persons with galactosemia, diagnostic challenge tests dependent on administering galactose orally or intravenously should not be used. Direct enzyme assay using erythrocytes establishes the diagnosis. One needs to confirm that the patient did not receive a blood transfusion before the collection of the blood sample, as a diagnosis could be missed. A novel method utilizes nonradioactive UV and high-performance liquid chromatography to accurately detect levels of galactose-1-phosphate uridyl transferase in erythrocytes.

**Genetics**

Transferase deficiency is an autosomal recessive disorder. Based on newborn screening in the United States, the frequency of the disease is approximately 1 in 47,000 live births. There are several enzymatic variants of galactosemia. The Duarte variant, a single amino acid substitution (p.N314D), has diminished red cell enzyme activity (50% of normal), but usually no clinical significance. This variant is the most common, with a carrier frequency of 12% in the general population. Those who are heterozygous for the Duarte variant of galactosemia typically have 25% of normal galactose activity, few symptoms, elevated metabolites, and no need for intervention. Other similar variants expressing little enzyme activity typically require no intervention. Some African-American patients have milder symptoms despite the absence of measurable transferase activity in erythrocytes; these patients retain 10% enzyme activity in liver and intestinal mucosa, whereas most white patients have no detectable activity in any of these tissues. More than 230 identifiable mutations have been associated with transferase deficiency. In African-Americans, 62% of alleles are represented by the p.S135L mutation, a mutation that is responsible for a milder disease course. In the white population, 70% of alleles are represented by the p.Q188R and p.K283N missense mutations and are associated with severe disease. Carrier testing and prenatal diagnosis can be performed by direct enzyme analysis of amniocytes or chorionic villi; testing can also be DNA based.

**Treatment and Prognosis**

Because of newborn screening for galactosemia, patients are being identified and treated early. Various non–lactose-containing milk substitutes are available (casein hydrolysates, soybean-based formula). Elimination of galactose from the diet along with adequate calcium supplementation reverses growth failure and renal and hepatic dysfunction. Cataracts regress, and most patients have no impairment of vision. Early diagnosis and treatment have improved the prognosis of galactosemia; however, on long-term follow-up, patients still manifest ovarian failure with primary or secondary amenorrhea, decreased bone mineral density, developmental delay, and learning disabilities that increase in severity with age. Hypergonadotrophic hypogonadism is reported in 80% to more than 90% of female patients with classic galactosemia. Although most women with classic galactosemia are infertile when they reach childbearing age, a small number have given birth. Most patients manifest speech disorders, whereas a smaller number demonstrate poor growth and impaired motor function and balance (with or without overt ataxia). The relative control of
Bibliography


GALACTOKINASE DEFICIENCY
The deficient enzyme is galactokinase, which normally catalyzes the phosphorylation of galactose. The principal metabolites accumulated are galactose and galactitol. Two genes are reported to encode galactokinase: GK1 on chromosome 17q24 and GK2 on chromosome 15. Cataracts are usually the sole manifestation of galactokinase deficiency; pseudotumor cerebri is a rare complication. The affected infant is otherwise asymptomatic. Heterozygote carriers may be at risk for presenile cataracts. Affected patients have an increased concentration of blood galactose levels, provided they have been fed a lactose-containing formula. The diagnosis is made by demonstrating an absence of galactokinase activity in erythrocytes or fibroblasts. Transferrase activity is normal. Treatment is dietary restriction of galactose.

URIDINE DIPHOSPHATE GALACTOSE-4-EPIMERASE DEFICIENCY
The abnormally accumulated metabolites are similar to those in transferrase deficiency; however, there is also an increase in cellular uridine diphosphate galactose. There are 2 distinct forms of epimerase deficiency. The first is a benign form discovered incidentally through neonatal screening programs. Affected persons are healthy and without problems; the enzyme deficiency is limited to leukocytes and erythrocytes. No treatment is required. The second form of epimerase deficiency is severe, and clinical manifestations resemble transferrase deficiency, with the additional symptoms of hypotonia and nerve deafness. The enzyme deficiency is generalized, and clinical symptoms respond to restriction of dietary galactose. Although this form of galactosemia is rare, it must be considered in a symptomatic patient with measurable galactose-1-phosphate who has normal transferrase activity. Diagnosis is confirmed by the assay of epimerase in erythrocytes.

Patients with the severe form of epimerase deficiency cannot synthesize galactose from glucose and are galactose-dependent. Because galactose is an essential component of many nervous system structural proteins, patients are placed on a galactose-restricted diet rather than a galactose-free diet.

Infants with the mild form of epimerase deficiency have not required treatment. It is advisable to follow urine specimens for reducing substances and exclude aminoaciduria within a few weeks of diagnosis while the infant is still on lactose-containing formula.

The gene for uridine diphosphate galactose-4-epimerase is located on chromosome 1 at 1p36. Carrier detection is possible by measurement of epimerase activity in the erythrocytes. Prenatal diagnosis for the severe form of epimerase deficiency, using an enzyme assay of cultured amniotic fluid cells, is possible.

Bibliography is available at Expert Consult.

87.3 Defects in Fructose Metabolism
Priya S. Kishnani and Yuan-Tsong Chen

Two inborn errors are known in the specialized pathway of fructose metabolism: benign or essential fructosuria and hereditary fructose intolerance (HFI). Fructose-1,6-bisphosphatase deficiency, although strictly speaking not a defect of the specialized fructose pathway, is discussed in Chapter 87.4.

DEFICIENCY OF FRUCTOKINASE (ESSENTIAL OR BENIGN FRUCTOSURIA)
Deficiency of fructokinase is not associated with any clinical manifestations. It is an accidental finding usually made because the asymptomatic patient’s urine contains a reducing substance. No treatment is necessary and the prognosis is excellent. Inheritance is autosomal recessive with an incidence of 1 in 120,000 live births. The gene encoding fructokinase is located on chromosome 2p23.3.

Fructokinase catalyzes the first step of metabolism of dietary fructose: conversion of fructose to fructose-1-phosphate (see Fig. 87.1). Without this enzyme, ingested fructose is not metabolized. Its level is increased in the blood, and it is excreted in urine because there is practically no renal threshold for fructose. Clinistest results reveal the urinary-reducing substance, which can be identified as fructose by chromatography.

DEFICIENCY OF FRUCTOSE-1,6-BISPHOSPHATE ALDOLASE (ALDOLASE B, HEREDITARY FRUCTOSE INTOLERANCE)
Deficiency of fructose-1,6-bisphosphate aldolase is a severe condition of infants that appears with the ingestion of fructose-containing food and is caused by a deficiency of fructose aldolase B activity in the liver, kidney, and intestine. The enzyme catalyzes the hydrolysis of fructose-1,6-bisphosphate into triose phosphate and glyceraldehyde phosphate. The same enzyme also hydrolyzes fructose-1-phosphate. Deficiency of this enzyme activity causes a rapid accumulation of fructose-1-phosphate and initiates severe toxic symptoms when exposed to fructose.

Epidemiology and Genetics
The true incidence of HFI is unknown but may be as high as 1 in every 26,000 live births. The gene for aldolase B is on chromosome 9q22.3. At least 40 mutations causing HFI are known. A single missense mutation, a G→C transition in exon 5 resulting in the normal alanine at position 149 being replaced by a proline, is the most common mutation identified in northern Europeans. This mutation, plus 2 other point mutations (p.A174D and p.N334K), account for 80–85% of HFI in Europe and the United States. Diagnosis of HFI can be made by direct DNA analysis and phosphorus magnetic resonance spectroscopy.

Clinical Manifestations
Patients with HFI are asymptomatic until fructose or sucrose (table sugar) is ingested (usually from fruit, fruit juice, or sweetened cereal). Symptoms may occur early in life, soon after birth if foods or formulas containing these sugars are introduced into the diet. Certain patients are very sensitive to fructose, whereas others can tolerate moderate intakes (up to 250 mg/kg/day). The average intake of fructose in Western societies is 1–2 g/kg/day. Early clinical manifestations resemble galactosemia and include jaundice, hepatomegaly, vomiting, lethargy, irritability, and convulsions. There may also be a higher incidence of celiac disease in HFI patients (>10%) than in the general population (1–3%). Laboratory findings include a prolonged clotting time, hypalbuminemia, elevation of bilirubin and transaminase levels, and proximal tubular dysfunction. Acute fructose ingestion produces symptomatic hypoglycemia; the higher the intake, the more severe is the clinical picture. Chronic ingestion results in failure to thrive and hepatic disease. If the intake of the fructose persists, hypoglycemic episodes recur, and liver and kidney failure progress, eventually leading to death.

Diagnosis
Suspicion of the enzyme deficiency is fostered by the presence of a reducing substance in the urine during an episode. The fructose challenge, although an effective method of diagnosis, causes a rapid fall, first of serum phosphate and then of blood glucose, and a subsequent increase in uric acid and magnesium. Because of high risks to the patient who can become acutely ill after the oral tolerance test, it should not be performed. Definitive diagnosis is made by assay of fructaldolase B activity in the liver. Gene-based diagnosis is available for most patients with this disease; a common mutation (substitution of Pro for Ala at position 149) accounts for 53% of HFI alleles worldwide.

Treatment
Treatment consists of the complete elimination of all sources of sucrose, fructose, and sorbitol from the diet. It may be difficult because these
Bibliography

sugars are widely used additives, found even in most medicinal preparations. With treatment, liver and kidney dysfunction improves, and catch-up in growth is common. Intellectual development is usually unimpaired. As the patient matures, symptoms become milder even after fructose ingestion; the long-term prognosis is good. Because of voluntary dietary avoidance of sucrose, affected patients have few dental caries.

Bibliography is available at Expert Consult.

87.4 Defects in Intermediary Carbohydrate Metabolism Associated with Lactic Acidosis

Priya S. Kishnani and Yuan-Tsong Chen

Lactic acidosis occurs with defects of carbohydrate metabolism that interfere with the conversion of pyruvate to glucose via the pathway of gluconeogenesis or to carbon dioxide and water via the mitochondrial enzymes of the Krebs cycle. Figure 87-4 depicts the relevant metabolic pathways. Type I GSD, fructose-1,6-diphosphatase deficiency, and phosphoenolpyruvate carboxylase deficiency are disorders of gluconeogenesis associated with lactic acidosis. Pyruvate dehydrogenase complex deficiency, respiratory chain defects, and pyruvate carboxylase deficiency are disorders in the pathway of pyruvate metabolism causing lactic acidosis. Lactic acidosis can also occur in defects of fatty acid oxidation, organic acidurias (see Chapters 85.6, 85.10, and 86.1), or biotin utilization diseases. These disorders are easily distinguishable by the presence of abnormal acylcarnitine profiles, amino acids in the blood, and unusual organic acids in the urine. Blood lactate, pyruvate, and acylcarnitine profiles and the presence of these unusual urine organic acids should be determined in infants and children with unexplained acidosis, especially if there is an increase of anion gap.

Lactic acidosis unrelated to an enzymatic defect occurs in hypoxemia. In this case, as well as in defects in the respiratory chain, the serum pyruvate concentration may remain normal (<1.0 mg/dL with an increased lactate:pyruvate ratio), whereas pyruvate is usually increased when lactic acidosis results from an enzymatic defect in gluconeogenesis or pyruvate dehydrogenase complex (both lactate and pyruvate are increased and the ratio is normal). Lactate and pyruvate should be measured in the same blood specimen and on multiple blood specimens obtained when the patient is symptomatic because lactic acidosis can be intermittent. Figure 87-5 is an algorithm for the differential diagnosis of lactic acidosis.

DISORDERS OF GLUCONEOGENESIS

Deficiency of Glucose-6-Phosphatase (Type I Glycogen Storage Disease)

Type I GSD is the only glycogenosis associated with significant lactic acidosis. The chronic metabolic acidosis predisposes these patients to osteopenia; after prolonged fasting, the acidosis associated with hypoglycemia is a life-threatening condition (see Chapter 87.1).

Fructose-1,6-Diphosphatase Deficiency

Fructose-1,6-diphosphatase deficiency impairs the formation of glucose from all gluconeogenic precursors, including dietary fructose. Hypoglycemia occurs when glycogen reserves are limited or exhausted. The clinical manifestations are characterized by life-threatening episodes of acidosis, hypoglycemia, hyperventilation, convulsions, and coma. In about half of the cases, the deficiency presents in the 1st wk of life. In infants and small children, episodes are triggered by febrile infections and gastroenteritis if oral food intake decreases. The frequency of the attacks decreases with age. Laboratory findings include low blood glucose, high lactate and uric acid levels, and metabolic acidosis. In contrast to HFI, there is usually no aversion to sweets; renal tubular and liver functions are normal.

The diagnosis is established by demonstrating an enzyme deficiency in either liver or intestinal biopsy. The enzyme defect can also be demonstrated in leukocytes in some cases. The gene coding for fructose-1,6-diphosphatase is located on chromosome 9q22; mutations are characterized, making carrier detection and prenatal diagnosis possible. Treatment of acute attacks consists of correction of hypoglycemia and acidosis by intravenous glucose infusion; the response is usually rapid. Avoidance of fasting, aggressive management of infections and restriction of fructose and sucrose from the diet can prevent further episodes. For long-term prevention of hypoglycemia, a slowly released carbohydrate such as cornstarch is useful. Patients who survive childhood develop normally.

![Figure 87-4](image-url) Enzymatic reactions of carbohydrate metabolism, deficiencies of which can give rise to lactic acidosis, pyruvate elevations, or hypoglycemia. The pyruvate dehydrogenase complex comprises, in addition to E1, E2, and E3, an extra lipoate-containing protein (not shown), called protein X, and pyruvate dehydrogenase phosphatase.

*a) pyruvate dehydrogenase component (E1) of the pyruvate dehydrogenase complex or,*

b) pyruvate decarboxylase; together with dihydrolipoyl-transacetylase (E2) and dihydrolipoyl-dehydrogenase, (E3), X protein and P.d. phosphatase it comprises the pyruvate dehydrogenase complex.


Phosphoenolpyruvate Carboxykinase Deficiency

Phosphoenolpyruvate carboxykinase (PEPCK) is a key enzyme in gluconeogenesis. It catalyzes the conversion of oxaloacetate to phosphoenolpyruvate (see Fig. 87-4). PEPCK deficiency is both a mitochondrial enzyme deficiency and a cytosolic enzyme deficiency, encoded by 2 distinct genes.

The disease has been reported in only a few cases. The clinical features are heterogeneous, with hypoglycemia, lactic acidemia, hepatomegaly, hypotonia, developmental delay, and failure to thrive as the major manifestations. There may be multisystem involvement, with neuromuscular deficits, hepatocellular damage, renal dysfunction, and cardiomyopathy. The diagnosis is based on the reduced activity of PEPCK in liver, fibroblasts, or lymphocytes. Fibroblasts and lymphocytes are not suitable for diagnosing the cytosolic form of PEPCK deficiency because these tissues possess only mitochondrial PEPCK. To avoid hypoglycemia, patients should be treated with slow-release carbohydrates such as cornstarch, and fasting should be avoided.

DISORDERS OF PYRUVATE METABOLISM

Pyruvate is formed from glucose and other monosaccharides, from lactate, and from alanine. It is metabolized through 4 main enzyme systems: lactate dehydrogenase, alanine aminotransferase, pyruvate carboxylase, and pyruvate dehydrogenase complex. Deficiency of the M subunit of lactate dehydrogenase causes exercise intolerance and myoglobinuria (see Chapter 87.1).

Pyruvate Dehydrogenase Complex Deficiency

After entering the mitochondria, pyruvate is converted into acetyl-CoA by the pyruvate dehydrogenase complex (PDHC), which catalyzes the oxidation of pyruvate to acetyl-CoA, which then enters the tricarboxylic acid cycle for ATP production. The complex comprises 5 components: \( E_1 \), an \( \alpha \)-ketoacid decarboxylase; \( E_2 \), a dihydrolipoyl transacylase; \( E_3 \), a dihydrolipoyl dehydrogenase; protein X, an extra lipoate-containing protein; and pyruvate dehydrogenase phosphatase. The most common is a defect in the \( E_1 \) (see Fig. 87-4).

Deficiency of the PDHC is the most common of the disorders leading to lactic acidemia and central nervous system dysfunction. The central nervous system dysfunction occurs because the brain obtains its energy primarily from oxidation of glucose. Brain acetyl-CoA is synthesized nearly exclusively from pyruvate.

The \( E_1 \) defects are caused by mutations in the gene coding for \( E_1 \) \( \alpha \) subunit, which is X-linked. Although X-linked, its deficiency is a problem in both males and females even though only 1 \( E_1 \) \( \alpha \) allele in females carries a mutation.

Clinical Manifestations

The disease has a wide spectrum of presentations from the most severe neonatal presentation to a mild late-onset form. The neonatal onset is associated with lethal lactic acidosis, white matter cystic lesions, agenesis of the corpus callosum, and the most severe enzyme deficiency. Infantile onset can be lethal or associated with psychomotor delay and chronic lactic acidosis, cystic lesions in the brainstem and basal ganglia, and pathologic features resembling Leigh disease (see below).
Neurologic symptoms in PDHC can be categorized into 2 groups: the first, abnormal brain development seen in both males and females, and the second, brain lesions and epilepsy seen in male patients only. Older children, usually boys, may have less acidosis, have greater enzyme activity, and manifest ataxia with high-carbohydrate diets. Intelligence may be normal. Patients of all ages may have facial dysmorphism, features similar to those of fetal alcohol syndrome.

The E1 and protein X-lipoate defects are rare and result in severe psychomotor retardation. The E1 lipoamide dehydrogenase defect leads to deficiency not only in the PDHC, but also in the tricarboxylic acid cycle and branched-chain ketoacid dehydrogenase complexes. This deficiency is more common in the Ashkenazi Jewish population. Recent studies suggest that the reactive oxygen species generated by the mutations responsible for lipoamide dehydrogenase deficiency may in fact explain certain disease characteristics and suggest the utility of antioxidant therapy. Pyruvate dehydrogenase phosphatase deficiency has also been reported. These other PDHC defects have clinical manifestations within the variable spectrum associated with PDHC deficiency due to E1 deficiency.

**Treatment**
The general prognosis is poor except in rare cases in which mutation is associated with altered affinity for thiamine pyrophosphate, which may respond to thiamine supplementation. Because carbohydrates can aggravate lactic acidosis, a ketogenic diet is recommended. The diet has been found to lower the blood lactate level; the long-term benefit to patient outcome is unclear. A potential treatment strategy is to maintain any residual PDHC in its active form by dichloroacetate, an inhibitor of E1 kinase. Beneficial effects of controlling postprandial lactic acidosis in some patients have been shown. Young children with congenital acidosis generally tolerate oral dichloroacetate well, but continued exposure is associated with peripheral neuropathy, a condition that could be attributable to the drug or the disease.

**Deficiency of Pyruvate Carboxylase**
Pyruvate carboxylase is a mitochondrial, biotin-containing enzyme essential in the process of gluconeogenesis; it catalyzes the conversion of pyruvate to oxaloacetate. The enzyme is also essential for Krebs cycle function as a provider of oxaloacetate and is involved in lipogenesis and formation of nonessential amino acids. Clinical manifestations of this deficiency have varied from neonatal severe lactic acidosis accompanied by hyperammonemia, citrullinemia, and hyperlysinemia (type B) to late-onset mild to moderate lactic acidosis and developmental delay (type A). In both types, patients who survived usually had severe psychomotor retardation with seizures, spasticity, and microcephaly. Some patients have pathologic changes in the brainstem and basal ganglia that resemble Leigh disease (see below). The clinical severity appears to correlate with the level of the residual enzyme activity. A "benign" form of pyruvate carboxylase deficiency characterized by recurrent attacks of lactic acidosis and mild neurologic deficits has also been described (type C). Laboratory findings are characterized by elevated levels of blood lactate, pyruvate, alanine, and ketonuria. In the case of type B, blood ammonia, citrulline, and lysine levels are also elevated, which might suggest a primary defect of the urea cycle. The mechanism is likely caused by depletion of oxaloacetate, which leads to reduced levels of aspartate, a substrate for argininosuccinate synthase in the urea cycle (see Chapter 85.12). The gene for pyruvate carboxylase is located on chromosome 11q13.4-q13.5 and approximately 15 mutations have been identified.

Treatment consists of avoidance of fasting, and eating a carbohydrate meal before bedtime. During acute episodes of lactic acidosis, patients should receive continuous intravenous glucose. Aspartate and citrate supplements restore the metabolic abnormalities; whether this treatment can prevent the neurologic deficits is not known. Liver transplantation has been attempted; its benefit remains unknown. Diagnosis of pyruvate carboxylase deficiency is made by the measurement of enzyme activity in liver or cultured skin fibroblasts and must be differentiated from holocarboxylase synthase or biotinidase deficiency.

**Deficiency of Pyruvate Carboxylase Secondary to Deficiency of Holocarboxylase Synthase or Biotinidase**
Deficiency of either holocarboxylase synthase (HCS) or biotinidase, which are enzymes of biotin metabolism, result in multiple carboxylase deficiency (pyruvate carboxylase and other biotin-requiring carboxylases and metabolic reactions) and in clinical manifestations associated with the respective deficiencies, as well as rash, lactic acidosis, and alopecia (see Chapter 85.6). The course of HCS or biotinidase deficiency can be protracted, with intermittent exacerbation of chronic lactic acidosis, failure to thrive, seizures, and hypotonia leading to spasticity, lethargy, coma, and death. Auditory and optic nerve dysfunction can lead to deafness and blindness, respectively. Late-onset milder forms have also been reported. Laboratory findings include metabolic acidosis and abnormal organic acids in the urine. In HCS deficiency, biotin concentrations in plasma and urine are normal. Diagnosis can be made in skin fibroblasts or lymphocytes by assay for HCS activity, and in the case of biotinidase, in the serum by a screening blood spot.

Treatment consists of biotin supplementation, 5-20 mg/day, and is generally effective if treatment is started before the development of brain damage. Patients identified through newborn screening and treated with biotin have remained asymptomatic.

Both enzyme deficiencies are autosomal recessive traits. The incidence of HCS deficiency is approximately 1 in 87,000 live births. HCS and biotinidase are located on chromosome 21q22 and 3p25, respectively. Ethnic-specific mutations in the HCS gene have been identified. Two common mutations (del7/ins3 and p.R538C) in the biotinidase gene account for 52% of all mutant alleles in symptomatic patients with biotinidase deficiency.

**Mitochondrial Respiratory Chain Defects (Oxidative Phosphorylation Disease)**
The mitochondrial respiratory chain catalyzes the oxidation of fuel molecules and transfers the electrons to molecular oxygen with concomitant energy transduction into ATP (oxidative phosphorylation). The respiratory chain produces ATP from adenosine diphosphate and inorganic phosphate utilizing the energy from electrons transferred from nicotinamide adenine dinucleotide (NADH) or flavin adenine dinucleotide and includes 5 specific complexes (I: NADH–coenzyme Q reductase; II: succinate–coenzyme Q reductase; III: coenzyme QH2, cytochrome C reductase; IV: cytochrome C oxidase; V: ATP synthase). Each complex is composed of 4–35 individual proteins and, with the exception of complex II (which is encoded solely by nuclear genes), is encoded by nuclear or mitochondrial DNA (inherited only from the mother by mitochondrial inheritance). Defects in any of these complexes or assembly systems produce chronic lactic acidosis presumably because of a change of the reduction-oxidation state with increased concentrations of NADH. In contrast to PDHC or pyruvate carboxylase deficiency, skeletal muscle and heart are usually involved in the respiratory chain disorders, and in muscle biopsy, "ragged red fibers" (indicating mitochondrial proliferation) are very suggestive when present (see Fig. 87-5). Because of the ubiquitous nature of oxidative phosphorylation, a defect of the mitochondrial respiratory chain accounts for a vast array of clinical manifestations and should be considered in patients in all age groups presenting with multisystem involvement. Some deficiencies resemble Leigh disease (see below), whereas others cause infantile myopathies such as MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes), MERRF (myoclonic epilepsy and ragged red fibers), and Kearns-Sayre syndrome (external ophthalmoplegia, acidosis, retinal degeneration, heart block, myopathy, and high cerebrospinal fluid protein) (Table 87-2; Chapters 598.2 and 611.4). There is a higher incidence of psychiatric disorders in adults with a primary oxidative phosphorylation disease than in the general population. Diagnosis requires demonstration of abnormalities of oxidative phosphorylation enzyme complex activities in tissues or of mitochondrial DNA or a nuclear gene coding for mitochondrial functions, or both (Fig. 87-6). Muscle histology, including
Table 87-2: Clinical and Genetic Heterogeneity of Disorders Related to Mutations in Mitochondrial DNA*

<table>
<thead>
<tr>
<th>SYMPTOMS, SIGNS, AND FINDINGS</th>
<th>LARGE DELETIONS IN mtDNA</th>
<th>MUTATION IN TRANSFER RNA</th>
<th>MUTATION IN RIBOSOMAL RNA</th>
<th>MUTATION IN MESSENGER RNA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KSS</td>
<td>PEO</td>
<td>PS</td>
<td>MERRF</td>
</tr>
<tr>
<td>CENTRAL NERVOUS SYSTEM</td>
<td></td>
<td></td>
<td></td>
<td>***</td>
</tr>
<tr>
<td>Seizures</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Ataxia</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Psychomotor regression</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>±</td>
</tr>
<tr>
<td>Hemiparesis and hemianopia</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Cortical blindness</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Migraine-like headaches</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Dystonia</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>PERIPHERAL NERVOUS SYSTEM</td>
<td>±</td>
<td>−</td>
<td>−</td>
<td>±</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUSCLE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weakness and exercise intolerance</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td></td>
</tr>
<tr>
<td>Ophthalmoplegia</td>
<td>+</td>
<td>±</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Ptosis</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>EYE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pigmentary retinopathy</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Optic atrophy</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>BLOOD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sideroblastic anemia</td>
<td>±</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>ENDOCRINE SYSTEM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>±</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Short stature</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
<td>±</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>HEART</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conduction disorder</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>±</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>±</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>GASTROINTESTINAL SYSTEM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exocrine pancreatic dysfunction</td>
<td>±</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Intestinal pseudoobstruction</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>EAR, NOSE, AND THROAT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensorineural hearing loss</td>
<td>±</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>KIDNEY</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fanconi syndrome</td>
<td>−</td>
<td>±</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>LABORATORY FINDINGS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactic acidosis</td>
<td>±</td>
<td>−</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ragged-red fibers on muscle biopsy</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>MODE OF INHERITANCE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Sporadic</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
</tbody>
</table>

*Characteristic constellations of symptoms and signs are bolded.
+ Presence of a symptom, sign, or finding; −, absence of a symptom, sign, or finding; ±, possible presence of a symptom, sign, or finding; AID, aminoglycoside-induced deafness; KSS, Kearns-Sayre syndrome; LHON, Leber’s hereditary optic neuropathy; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged-red fibers; MILS, maternally inherited Leigh syndrome; mtDNA, mitochondrial DNA; NARP, neuropathy, ataxia, and retinitis pigmentosa; PEO, progressive external ophthalmoplegia; PS, Pearson syndrome.


Electron microscopy can detect ragged red fibers and other abnormalities typical of mitochondrial myopathies. Analysis of oxidative phosphorylation complexes I-IV from intact mitochondria isolated from fresh skeletal muscle is the most sensitive assay for mitochondrial disorders; however, electron transport chain testing of flash-frozen muscle provides an alternative approach when fresh muscle testing is not available. Next-generation sequencing of mitochondrial DNA and panels of nuclear genes provides a noninvasive alternative to diagnosis, albeit with lower sensitivity. Specific criteria may assist in making a diagnosis (Table 87-3). Table 87-4 lists clues to the diagnosis of mitochondrial diseases.

Treatment remains largely symptomatic and does not significantly alter the outcome of disease. Some patients appear to respond to cofactor supplements, typically coenzyme Q10 ± l-carnitine at pharmacologic doses. The addition of creatine monohydrate and α-lipoic acid supplementation may add a significant benefit.
Leigh Disease (Subacute Necrotizing Encephalomyelopathy)

Leigh disease is a heterogenous neurologic disease that remains a neuropathologic description characterized by demyelination, gliosis, necrosis, relative neuronal sparing, and capillary proliferation in specific brain regions. In decreasing order of severity, the affected areas are the basal ganglia, brainstem cerebellum, and cerebral cortex (see Chapter 598). The classic presentation is of an infant who presents with central hypotonia, developmental regression or arrest, and signs of brainstem or basal ganglia involvement. The clinical presentation is highly variable. Diagnosis is usually confirmed by radiologic or pathologic evidence of symmetric lesions affecting the basal ganglia, brainstem, and subthalamic nuclei. Patients with Leigh disease have defects in several enzyme complexes. Dysfunction in cytochrome C oxidase (complex IV) is the most commonly reported defect, followed by NADH-coenzyme Q reductase (complex I), PDHC, and pyruvate carboxylase. Mutations in the nuclear SURF1 gene, which encodes a factor involved in the biogenesis of cytochrome C oxidase and mitochondrial DNA mutations in the adenosine triphosphatase 6 coding region, are common molecular findings in patients with Leigh disease. Patients with Leigh disease frequently present with developmental delay, seizures, altered consciousness, failure to thrive, pericardial effusion, and dilated cardiomyopathy. The prognosis for Leigh syndrome is poor. In a study of 14 cases, there were 7 fatalities before the age of 1.5 yr.

Lactic acidosis, hypoglycemia, and encephalopathy have also been reported in patients with thiamine transporter deficiency and with pyridoxine-dependent epilepsy. Both disorders should improve by the provision of thiamine and pyridoxine, respectively.

Bibliography is available at Expert Consult.
neonatal hypotonia, and neonatal hypertonia as minor clinical criteria. Appropriate testing.


<table>
<thead>
<tr>
<th>Table 87-3</th>
<th>Modified Walker Criteria Applied to Children Referred for Evaluation of Mitochondrial Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MAJOR CRITERIA</strong></td>
<td><strong>MINOR CRITERIA</strong></td>
</tr>
<tr>
<td>Clinical</td>
<td>Clinically complete RC encephalomyopathy* or a mitochondrial cytopathy defined as fulfilling 3 criteria†</td>
</tr>
<tr>
<td>Histology</td>
<td>&gt;2% RRF in skeletal muscle</td>
</tr>
<tr>
<td>Enzymology</td>
<td>Cytochrome c oxidase–negative fibers or residual activity of an RC complex &lt;20% in a tissue; &lt;30% in a cell line, or &lt;30% in 2 or more tissues</td>
</tr>
<tr>
<td>Functional</td>
<td>Fibroblast ATP synthesis rates &gt;3 SD below mean</td>
</tr>
<tr>
<td>Molecular</td>
<td>Nuclear or mtDNA mutation of undisputed pathogenicity</td>
</tr>
<tr>
<td>Metabolic</td>
<td>One or more metabolic indicators of impaired metabolic function</td>
</tr>
</tbody>
</table>

*Leigh disease, Alpers disease, lethal infantile mitochondrial disease, Pearson syndrome, Kearns-Sayre syndrome, MELAS (myopathy, encephalopathy, lactic acidosis, and stroke-like episodes), MERRF (myoclonic epilepsy associated with ragged red fibers), NARP (neuropathy, ataxia and retinitis pigmentosa), MNGIE (mitochondrial neurogastrointestinal encephalomyopathy), and LHON (Leber hereditary optic neuropathy).

†(1) Unexplained combination of multisystemic symptoms that is essentially pathognomonic for an RC disorder; (2) a progressive clinical course with episodes of exacerbation or a family history strongly indicative of an mtDNA mutation, and (3) other possible metabolic or nonmetabolic disorders have been excluded by appropriate testing.

‡Added pediatric features: stillbirth associated with a paucity of intrauterine movement, neonatal death or collapse, movement disorder, severe failure to thrive, neonatal hypotonia, and neonatal hypertonia as minor clinical criteria.

ATP, adenosine triphosphate; mtDNA, mitochondrial DNA; RC, respiratory chain; RRF, ragged red fibers; SSAM, subsarcolemmal accumulation of mitochondria.


<table>
<thead>
<tr>
<th>Table 87-4</th>
<th>Clues to the Diagnosis of Mitochondrial Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NEUROLOGIC</strong></td>
<td>Cerebral stroke-like lesions in a nonvascular pattern</td>
</tr>
<tr>
<td>Basal ganglia disease</td>
<td>Encephalopathy; recurrent or with low/moderate dosing of valproate</td>
</tr>
<tr>
<td>Neurodegeneration</td>
<td>Epilepsia partialis continua</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>Ataxia</td>
</tr>
<tr>
<td>MRI findings consistent with Leigh disease</td>
<td>Characteristic MRS peaks</td>
</tr>
<tr>
<td>Lactate peak at 1.3 ppm TE (time to echo) at 35 and 135</td>
<td>Succinate peak at 2.4 ppm</td>
</tr>
<tr>
<td><strong>CARDIOVASCULAR</strong></td>
<td>Hypertrophic cardiomyopathy with rhythm disturbance</td>
</tr>
<tr>
<td>Unexplained heart block in a child</td>
<td>Cardiomyopathy with lactic acidosis (&gt;5 mM)</td>
</tr>
<tr>
<td>Dilated cardiomyopathy with muscle weakness</td>
<td>Wolff-Parkinson-White arrhythmia</td>
</tr>
<tr>
<td><strong>OPHTHALMOLOGIC</strong></td>
<td>Retinal degeneration with signs of night blindness, color vision deficits, decreased visual acuity, or pigmentary retinopathy</td>
</tr>
<tr>
<td>Ophthalmoplegia/pareisis</td>
<td>Fluctuating, dysconjugate eye movements</td>
</tr>
<tr>
<td>Ptosis</td>
<td>Sudden- or insidious-onset optic neuropathy/atrophy</td>
</tr>
<tr>
<td><strong>GASTROENTEROLOGIC</strong></td>
<td>Unexplained or valproate-induced liver failure</td>
</tr>
<tr>
<td>Severe dysmotility</td>
<td>Pseudoobstructive episodes</td>
</tr>
<tr>
<td><strong>OTHER</strong></td>
<td>A newborn, infant, or young child with unexplained hypotonia, weakness, failure to thrive, and a metabolic acidosis (particularly lactic acidosis)</td>
</tr>
<tr>
<td>Exercise intolerance that is not in proportion to weakness</td>
<td>Hypersensitivity to general anesthesia</td>
</tr>
<tr>
<td>Episodes of acute rhahdomyolysis</td>
<td></td>
</tr>
</tbody>
</table>

Approximately 90% of glucose metabolism in the body is via the glycolytic pathway, with the remaining 10% via the hexose monophosphate pathway. The hexose monophosphate shunt leads to formation of pentoses, as well as providing NADH. One of the metabolites is ribose-5-phosphate, which is used in the biosynthesis of ribonucleotides and deoxyribonucleotides. Through the transketolase and transaldolase reactions, the pentose phosphates can be converted back to fructose-6-phosphate and glucose-6-phosphate.

**ESSENTIAL PENTOSURIA**

Essential pentosuria is a benign disorder encountered principally in Ashkenazi Jews and is an autosomal recessive trait. The urine contains 1-xylulose, which is excreted in increased amounts because of a block in the conversion of 1-xylulose to xylitol as a result of xylitol dehydrogenase deficiency. The condition is usually discovered accidentally in a urine test for reducing substances; no treatment is required.

**Transaldolase Deficiency**

Few patients have reported symptoms that include liver cirrhosis, hepatosplenomegaly, severe neonatal hepatopathy, and cardiomyopathy. Biochemical abnormalities revealed elevated levels of arabitol, ribitol, and erythritol in the urine. Most recently, erythronic acid has been identified by urine nuclear magnetic resonance spectroscopy as another hallmark metabolite. Enzyme assay in the lymphoblasts and fibroblasts demonstrated low transaldolase activity, which was confirmed by mutations in the transaldolase gene. In addition, measurement of transaldolase activity in fibroblasts, lymphoblasts, or liver tissue, as well as assessing urinary concentrations of polyols also can be used to confirm the diagnosis.

**Ribose-5-Phosphate Isomerase Deficiency**

Only 1 case of this disorder has been reported. The affected male had psychomotor delay from early in life and developed epilepsy at 4 yr of age. Thereafter, a slow neurologic regression developed, with prominent cerebellar ataxia, some spasticity, optic atrophy, and a mild sensorimotor neuropathy. MRI of the brain at ages 11 yr and 14 yr showed
Bibliography
extensive abnormalities of the cerebral white matter. Proton magnetic
resonance spectroscopy (MRS) of the brain revealed elevated levels of
ribitol and D-arabitol. These pentitols were also increased in urine and
plasma similar to the patient found in transaldolase deficiency. Enzyme
assays in cultured fibroblasts showed deficient ribose-5-phosphate
isomerase activity, which was confirmed by a molecular study. These
results combined with a study of ribose-5-phosphate isomerase-
deficient mice converged to demonstrate that the specific genetic
pairing of a null allele with an allele coding for a form of the enzyme
that is only partly active, allowing for cell-type-dependent expression
deficits, is a contributing factor to the rarity of the disease. Ribose-5-
phosphate isomerase deficiency may represent an example of a single-
gene disease that appears seldom because of its complex molecular
etiology.

Bibliography is available at Expert Consult.

87.6 Disorders of Glycoprotein
Degradation and Structure
Margaret M. McGovern and Robert J. Desnick

The disorders of glycoprotein degradation and structure include
several lysosomal storage diseases that result from defects in glycopro-
tein degradation, and the congenital disorders of glycosylation (CDGs),
which are pathophysiologically unrelated. Glycoproteins are macro-
molecules that are composed of oligosaccharide chains linked to a
peptide backbone. They are synthesized by 2 pathways: the glycosyl-
transferase pathway, which synthesizes oligosaccharides linked
O-glycosidically to serine or threonine residues; and the dolichol,
lipid-linked pathway, which synthesizes oligosaccharides linked N-
glycosidically to asparagine.

The glycoprotein lysosomal storage diseases result from the defi-
cency of the enzymes that normally participate in the degradation of
oligosaccharides and include sialidosis, galactosialidosis, aspartylglu-
cosaminuria, and α-mannosidosis. In some instances, the underlying
abnormality that leads to glycoprotein accumulation also results in
abnormal degradation of other classes of macromolecules that contain
similar oligosaccharide linkages, such as certain glycolipids and pro-
teglycans. In these instances, the underlying enzymatic deficiency
results in the accumulation of both glycoproteins and glycolipids. The
classification of these types of disorders as lipidoses or glycoprotein-
degradation disorders depends on the nature of the predominantly stored substance.
In general, the glycoprotein disorders are characterized by autosomal
recessive inheritance and a progressive disease course with clinical
features that resemble those seen in the mucopolysaccharidoses.

SIALIDOSIS AND GALACTOSIALIDOSIS
Sialidosis is an autosomal recessive disorder that results from the
primary deficiency of neuraminidase because of mutations in the gene
that encodes this protein, which is located on chromosome 10. In
contrast, galactosialidosis is caused by the deficiency of 2 lysosomal
enzymes—neuraminidase and β-galactosidase. The loss of these enzy-
matic activities results from mutations in a gene located on chromo-
some 20 that encodes protective protein/cathepsin A, which functions
to stabilize these enzymatic activities. Neuraminidase normally cleaves
terminal sialyl linkages of several oligosaccharides and glycoproteins.
Its deficiency results in the accumulation of oligosaccharides, and the
urinary excretion of sialic acid terminal oligosaccharides and sialyl-
glycoproteins. Examination of tissues from affected individuals reveals
pathologic storage of substrate in many tissues including liver, bone
marrow, and brain.

The clinical phenotype associated with neuraminidase deficiency is
variable and includes type I sialidosis, which usually presents in the 2nd
decade of life with myoclonus and the presence of a cherry-red spot.
These patients typically come to attention secondary to gait distur-
bances, myoclonus, or visual complaints. In contrast, type II sialidosis
occurs as congenital, infantile, and juvenile forms. The congenital and
infantile forms result from isolated neuraminidase deficiency, whereas
the juvenile form results from both neuraminidase and β-galactosidase
deficiency. The congenital type II disease is characterized by hydrops
fetalis, neonatal ascites, hepatosplenomegaly, stippling of the epiphy-
ses, periosteal cloaking, and stillbirth or death in infancy. The type II
infantile form presents in the 1st yr of life with dysostosis multiplex,
moderate intellectual disability, visceromegaly, corneal clouding,
cherry red spot, and seizures. The juvenile type II form of sialidosis,
which is sometimes designated galactosialidosis, has a variable age of
onset ranging from infancy to adulthood. In infancy, the phenotype is
similar to that of GM, gangliosidosis, with edema, ascites, skeletal
dysplasia, and cherry-red spot. Patients with later-onset disease have
dysostosis multiplex, visceromegaly, mental retardation, dysmorphism,
corneal clouding, progressive neurologic deterioration, and bilateral
cherry red spots. No specific therapy exists for any form of the disease,
although studies in animal models have demonstrated improvement in
the phenotype after bone marrow transplantation. The diagnosis of
sialidosis and galactosialidosis is achieved by the demonstration of the
specific enzymatic deficiency. Prenatal diagnosis using cultured amni-
otic cells is also possible.

ASPARTYLGLUCOSAMINURIA
This is a rare autosomal recessive lysosomal storage disorder, except in
Finland, where the carrier frequency is estimated at 1 in 36 adults. The
disorder results from the deficient activity of aspartylglucosaminidase
and the subsequent accumulation of aspartylglucosamine, particularly
in the liver, spleen, and thyroid. The gene for the enzyme has been
localized to the long arm of chromosome 4 and the complementary
DNA has been cloned and sequenced. In the Finnish population, a
single mutation in the gene (C163S) accounts for most mutant alleles,
whereas outside of Finland, a large number of private mutations have
been described. Affected individuals with aspartylglucosaminuria typi-
cally present in the 1st yr of life with recurrent infections, diarrhea,
and hernias. Coarsening of the facies and short stature usually develop
later. Other features include joint laxity, macroglossia, hoarse voice,
crystal-like lens opacities, hypotonia, and spasticity. Psychomotor
development is usually near normal until the age of 5 yr when a decline
is noted. Behavioral abnormalities are typical and IQ values in affected
adults are usually <40. Survival to adulthood is common, with most
early deaths attributable to pneumonia or other pulmonary causes.
Definitive diagnosis requires measurement of the enzyme in peripheral
blood leukocytes. Molecular diagnosis by analysis of DNA for the
C163S mutation is possible for Finnish patients. Several patients have
undergone allogeneic bone marrow transplants with some reports of
stabilization of the neurologic phenotype, but this approach has not
been proven effective and no specific treatment is available. Prenatal
diagnosis by the determination of the level of aspartylglucosaminidase
in cultured amniocytes or chorionic villi has been reported.

α-MANNOSIDOSIS
This autosomal recessive disorder results from the deficient activity of
α-mannosidase and the accumulation of mannose-rich compounds.
The gene encoding the enzyme has been localized to chromosome
19p13.2-q12, although the complementary DNA has not been cloned.
Affected patients with this disorder display clinical heterogeneity.
There is a severe infantile form, or type I disease, and a milder juvenile
variant, type II disease. All patients have psychomotor retardation,
facial coarsening, and dysostosis multiplex. The infantile form of the
disorder, however, is characterized by more rapid cognitive deteriora-
tion, with death occurring between the ages of 3 and 10 yr. Patients
with the infantile form also have more severe skeletal involvement and
hepatosplenomegaly. The juvenile disorder is characterized by onset of
symptoms in early childhood or adolescence with milder somatic fea-
tures and survival to adulthood. Hearing loss, destructive synovitis,
pancytopenia, and spastic paraplegia have been reported in type II
patients. No specific therapy exists for the disorder. The diagnosis is
made by the demonstration of the deficiency of α-mannosidase activity
in white blood cells or cultured fibroblasts, and prenatal diagnosis has
also been achieved.
Bibliography

Defects of Protein N-Glycosylation

<table>
<thead>
<tr>
<th>DEFECTS OF PROTEIN N-GLYCOSYLATION</th>
<th>CLINICAL FEATURES</th>
<th>DIAGNOSTIC APPROACH</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMM2-CDG (CDG-Ia)</td>
<td>Dysmorphic facial features, abnormal lipid distribution, strabismus, protein-losing enteropathy, frequent vomiting, failure to thrive, short stature, cardiomyopathy, pericardial fluid collection, proteinuria, hepatomegaly, liver cirrhosis, hypotonia, ataxia, speech delay, mental retardation, seizures, cataract, retinitis pigmentosa, visual loss, peripheral neuropathy, hypothyreosis, thrombosis, bleeding anomalies, osteoporosis, recurrent infections, thrombocytopenia</td>
<td>Screening by TIEF, confirming type I or type II pattern. In type I, measurement of PMM and PMI enzyme activity in leukocytes or fibroblasts. In case of normal results of PMM/PMI, lipid-linked oligosaccharides analysis in fibroblasts. In type II, mass spectrometry of isolated serum N-glycans or serum apoC-III isoelectrofocusing. Based on the findings, choose appropriate genetic testing. Normal TIEF results* necessitate direct mutation analysis</td>
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<tr>
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<td>ALG6-CDG (CDG-ic)</td>
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</tr>
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<td>GC51-CDG (CDG-IIb)</td>
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Defects of Protein O-Glycosylation

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<th>CLINICAL FEATURES</th>
<th>DIAGNOSTIC APPROACH</th>
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<tbody>
<tr>
<td>EXT1/EXT2-CDG</td>
<td>Multiple exostosis; short stature/joint laxity/progeria; familial tumoral calcinosis; skeletal dysplasia; muscle dystrophy; brain developmental defect; spondylocoelostal dystostosis; congenital eye anomalies/cataract</td>
<td>Syndromic presentation and organ-specific diagnosis of the disease necessitates a genetic approach; upon suspicion perform direct mutation analysis</td>
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<td>B4GALT7-CDG</td>
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Defects of Glycosphingolipid and GPI-Anchor Glycosylation

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<th>CLINICAL FEATURES</th>
<th>DIAGNOSTIC APPROACH</th>
</tr>
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<td>SiAT9-CDG</td>
<td>Epilepsy; hepatomegaly/portal vein thrombosis; hyperphosphatasa, mental retardation</td>
<td>Mutation analysis. Expression analysis of glycosphingolipidositol-linked proteins (e.g., CD59 or CD24) on hematopoietic cells</td>
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<td>PIcM-CDG</td>
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<td>PIGV-CDG</td>
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Defects of Multiple Glycosylation and Other Pathways

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<th>CLINICAL FEATURES</th>
<th>DIAGNOSTIC APPROACH</th>
</tr>
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<tbody>
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<td>DPM1-CDG (CDG-Ie)</td>
<td>Dysmorphic facial features, strabismus; cardiomyopathy, muscle dystrophy; hepatomegaly; recurrent infections; thrombosis/bleeding anomalies; hypotonia, mental retardation, seizures; cardiomyopathy; ichthyosis, ataxia, visual loss; skeletal dysplasia; hyperthermia, adducted thumbs; failure to thrive; cutis laxa; HEMPAS</td>
<td>Screening by TIEF, confirming type I or type II pattern. In type II pattern, additional apoC-III isoelectric focusing. In patients with normal TIEF, if there is a syndromic presentation upon suspicion perform direct mutation analysis. In patients with muscle dystrophy perform dystroglycan staining in muscle biopsy, in a syndromic presentation upon suspicion direct mutation analysis</td>
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<td>DPM3-CDG (CDG-Io)</td>
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<td>MPDUL1-CDG (CDG-If)</td>
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<tr>
<td>GNE-CDG</td>
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<tr>
<td>B4GALT1-CDG (CDG-Ig)</td>
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<td>SLC35A1-CDG (CDG-IIh)</td>
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</tr>
<tr>
<td>SLC35C1-CDG (CDG-IIc)</td>
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<td>DK1-CDG (CDG-Im)</td>
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<tr>
<td>SRGAS3-CDG (CDG-Iq)</td>
<td></td>
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</tr>
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<td>COG-CDG (COG1, COG4, COG5, COG6, COG7, COG 8)</td>
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<td>SEC23B-CDG</td>
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</table>

Previous congenital disorders of glycosylation nomenclature are in parentheses.

*Normal TIEF results can be due to young age or also in GCS1-CDG, SLC35C1-CDG and SLC35A1-CDG.

Apo, apolipoprotein; GPI, glyosphingolipidositol; HEMPAS, hereditary erythroblastotic multinuclearity with a positive acidified serum; PMI, phosphomannomutase; TIEF, transferrin isoelectric focusing.


CONGENITAL DISORDERS OF GLYCOSYLATION

These are a heterogeneous group of autosomal recessive disorders that result from defective protein and lipid glycosylation. The protein glycosylation disorders result from defects of N-glycosylation, combined N- and O-glycosylation, the dolichol pathway and the conserved oligomeric Golgi complex. The more recently discovered lipid-glycosylation disorders include defects of ganglioside synthesis (GM3 synthase deficiency) and the glycosphingolipidositol anchor system. In addition, there are patients with glycosylation defects for which the molecular and biochemical bases are not yet known.

To date, more than 30 CDG subtypes have been identified (Table 87-5). In general, most CDG disorders are multisystemic and present with variable involvement of the central nervous system (most often hypotonia and ataxia), abnormal fat distribution, ocular movement defects, coagulation abnormalities, gastrointestinal symptoms including protein-losing enteropathy, retinitis pigmentosa, hormonal abnormalities, and, in some cases, dysmorphic features. CDG type Ia, which results from mutations in the gene that encodes phosphomannomutase, is the most common form. The most consistent clinical features of this disorder include variable degrees of psychomotor retardation, subcutaneous fat pads and inverted nipples. Frequent neurologic findings in infancy include cerebellar atrophy (Fig. 87-7), hypotonia, weakness, hyperreflexia, and stroke-like episodes (Table 87-6).

In childhood, ataxia, muscle atrophy, decreased deep tendon reflexes, toe walking, and continued stroke-like episodes are observed. The latter events may be related to coagulopathies characterized by reduced antithrombin III and proteins C and S, in conjunction with abnormal levels of factors VIII, IX, XI, and XIII, which together increase risk for bleeding and thrombosis. Growth failure, liver dysfunction, retinal
<table>
<thead>
<tr>
<th>NAME</th>
<th>DEFECT</th>
<th>DYSMORPHOLOGY</th>
<th>NEUROLOGIC SIGNS</th>
<th>GASTROINTESTINAL SIGNS</th>
<th>OTHER SIGNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDG-Ia</td>
<td>Phosphomannomutase 2</td>
<td>Fat maldistribution: narrow waist, fat in axilla, groin, buttock High nasal bridge Prominent jaw Large ears Inverted nipples</td>
<td>Hypotonia Hyporeflexia Strabismus Ataxia: olivopontocerebellar atrophy or hypoplasia Mental retardation (IQ 40-60) Stroke-like episodes Hemorrhagic cerebral infarcts Polynuropathy Muscle wasting Scoliosis Spinal stenosis Kyphosis Pigmentary retinal degeneration Contractures Seizures</td>
<td>Poor feeding, failure to thrive Carnitine deficiency Diarrhea Liver failure</td>
<td>Cardiomyopathy Pericardial effusions Nephrotic syndrome Renal tubulopathy Severe infections Hypogonadism Absent puberty TBG deficiency ↓ Levels of: antithrombin III, α1-acid glycoprotein, α1-antitrypsin, ferritin, ceruloplasmin, proteins C + S, factor XI, complement C1, C3a, C4a</td>
</tr>
<tr>
<td>CDG-Ib</td>
<td>Phosphomannose isomerase</td>
<td>None</td>
<td>Normal development</td>
<td>Protein-losing enteropathy Failure to thrive Chronic intractable diarrhea Hepatic fibrosis Hyperinsulinemic hypoglycemia Vomiting</td>
<td>Coagulopathy ↓ Proteins C, S, antithrombin III</td>
</tr>
<tr>
<td>CDG-Ic</td>
<td>Glucosyltransferase</td>
<td>None</td>
<td>Similar to CDG-Ia but milder Mild cerebellar hypoplasia Seizures</td>
<td>Failure to thrive</td>
<td>Frequent infections Coagulopathy Failure to thrive Recurrent eyelid edema Pigmentary retinal degeneration</td>
</tr>
<tr>
<td>CDG-IId</td>
<td>Mannosyltransferase</td>
<td>High-arched palate</td>
<td>Microcephaly Seizures (severe) Developmental delay CNS atrophy</td>
<td>Failure to thrive</td>
<td>Coagulopathy</td>
</tr>
<tr>
<td>CDG-Ie</td>
<td>Dolichol-phosphate-mannose synthetase Failure to thrive</td>
<td>High-arched palate Down-slooting palpebral fissures Hemangiomias Short arms Small hands Dysplastic nails</td>
<td>Microcephaly Hypotonia Developmental delay Seizures (severe) Cortical blindness Hyperreflexia Delayed myelination</td>
<td>Failure to thrive</td>
<td>↑ CPK</td>
</tr>
<tr>
<td>CDG-IIa</td>
<td>N-acetyl-glucosaminyltransferase II</td>
<td>Facial dysmorphology</td>
<td>Stereotypic hand movements Seizures Developmental delay No neuropathy or cerebellar hypoplasia</td>
<td>Failure to thrive</td>
<td>Coagulopathy</td>
</tr>
<tr>
<td>CDG-IIb</td>
<td>Glucosidase I</td>
<td>Facial dysmorphology</td>
<td>Hypotonia Retardation Seizures</td>
<td>Hepatomegaly</td>
<td>Coagulopathy</td>
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<tr>
<td>CDG-IIc</td>
<td>GDP-fucose transporter I</td>
<td>Facial dysmorphology</td>
<td>Developmental delay Hypotonia</td>
<td>Failure to thrive</td>
<td>Recurrent infections with leukocytosis</td>
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<tr>
<td>CDG-x or CDG-Ix</td>
<td>Unknown</td>
<td>Like CDG-Ia Microcephaly</td>
<td>Hypotonia Seizures Cerebellar hypoplasia Developmental delay</td>
<td>Intractable diarrhea Failure to thrive</td>
<td>Nonimmune hydrops Cataracts Thrombocytopenia Renal tubulopathy Distal bone demineralization</td>
</tr>
<tr>
<td>CDG-Ih</td>
<td>Glucosyltransferase 2</td>
<td>Facial dysmorphology</td>
<td>Seizures Hypotonia Developmental delay</td>
<td>Chronic diarrhea Protein-losing enteropathy Chronic liver disease</td>
<td>Coagulopathy Renal microcyts Nephrotic syndrome</td>
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<tr>
<td>CDG-X variant</td>
<td>Unknown</td>
<td>None</td>
<td>None</td>
<td>Asymptomatic cryptogenic Chronic liver disease</td>
<td>Coagulopathy</td>
</tr>
</tbody>
</table>
Figure 87-7 Sagittal T2-weighted MR image shows severe spinal cord compression with myelopathy (white arrow), together with cerebellar atrophy (black arrow), and cortical atrophy of the parietal lobe (red arrow). (From Schade van Westrum SM, Nederkoorn PJ, Schuurman PR, et al: Skeletal dysplasia and myelopathy in congenital disorder of glycosylation type 1A, J Pediatr 148:115–117, 2006, Fig. 1.)

degeneration, and skeletal abnormalities have also been described. The skeletal features can include contractures, kyphoscoliosis, and pectus carinatum, all of which may be secondary to the neurologic effects of the disorder. Pericardial effusion in older patients and hypertrophic obstructive cardiomyopathy in the infant also may occur.

Among the other types, few have distinctive phenotypes. These include CDG-Ib, which is characterized by protein-losing enteropathy and normal neurologic function; CDG-If, which includes ichthyosis and growth retardation; and CDG-IIf, in which macrothrombocytopenia is present.

Diagnostic testing for CDG types that result from defects of N-glycosylation begins with isoelectric focusing of N-glycosylated serum transferrin. For some types further confirmation of the diagnosis by enzymatic analysis in fibroblasts or leukocytes and/or mutation analysis of the relevant gene is available. Although prenatal diagnosis by analysis of transferrin has been attempted, it has not proven reliable. Treatment of these disorders is symptomatic, except for CDG-Ib, which responds to oral mannose (100-150 mg/kg/day every 4-6 hr).

Bibliography is available at Expert Consult.
Bibliography
Mucopolysaccharidoses are hereditary, progressive diseases caused by mutations of genes coding for lysosomal enzymes needed to degrade glycosaminoglycans (acid mucopolysaccharides). Glycosaminoglycans (GAGs) are long-chain complex carbohydrates composed of uronic acids, amino sugars, and neutral sugars. The major GAGs are chondroitin-4-sulfate, chondroitin-6-sulfate, heparan sulfate, dermatan sulfate, keratan sulfate, and hyaluronan. These substances are synthesized and, with the exception of hyaluronan, linked to proteins to form proteoglycans, major constituents of the ground substance of connective tissue, of nuclear and cell membranes. Degradation of proteoglycans starts with the proteolytic removal of the protein core followed by the stepwise degradation of the glycosaminoglycan moiety. Failure of this degradation because of absent or grossly reduced activity of mutated lysosomal enzymes results in the intralysosomal accumulation of glycosaminoglycan fragments (Fig. 88-1). Distended lysosomes accumulate in the cell, interfere with cell function and lead to characteristic pattern of clinical, radiologic, and biochemical abnormalities (Table 88-1, Fig. 88-2). Within this pattern, specific diseases can be recognized which evolve from the intracellular accumulation of different degradation products (Table 88-2). As a general rule, the impaired degradation of heparan sulfate is more closely associated with intellectual disability, and the impaired degradation of dermatan sulfate, chondroitin sulfates, and keratan sulfate with mesenchymal abnormalities. Variable expression within a given entity results from allelic mutations and varying residual activity of mutated enzymes. For instance, allelic mutations of the gene encoding L-iduronidase may result in severe Hurler disease with early death or in mild Scheie disease manifesting only with limited joint mobility, mild skeletal abnormalities and corneal opacities. Mucopolysaccharidoses are autosomal recessive disorders with the exception of Hunter disease, which is X-linked recessive. Their overall frequency is between 3.5 in 100,000 births and 4.5 in 100,000 births. The most common subtype is MPS-III, followed by MPS-I and MPS-II.

CLINICAL ENTITIES
Mucopolysaccharidosis I
Mucopolysaccharidosis (MPS)-I is caused by mutations of the IDUA gene on chromosome 4p16.3 encoding α-L-iduronidase. Mutation analysis has revealed 2 major alleles, W402X and Q70X, account for more than half the MPS-I alleles in the white population. The
Part XI ♦ Metabolic Disorders

Hurler Disease

This form of MPS-I (MPS-IH) is a severe, progressive disorder with multiple organ and tissue involvement that results in premature death, usually by 10 yr of age. An infant with Hurler syndrome appears normal at birth, but inguinal herniae are often present. Diagnosis is usually made between 6 and 24 mo with evidence of hepatosplenomegaly, coarse facial features, corneal clouding, large tongue, prominent forehead, joint stiffness, short stature, and skeletal dysplasia. Acute cardiomyopathy has been found in some infants younger than 1 yr of age. Most patients have recurrent upper respiratory tract and

mutations introduce stop codons with ensuing absence of functional enzyme (null alleles) and in homozygosity or compound heterozygosity give rise to Hurler disease. Other mutations occur in only 1 or a few individuals.

Deficiency of α-L-iduronidase results in a wide range of clinical involvement from severe Hurler disease to mild Scheie disease, which are ends of a broad clinical spectrum. Homozygous nonsense mutations result in severe forms of MPS-I, whereas missense mutations are more likely to preserve some residual enzyme activity associated with a milder form of the disease.

Figure 88-1 Degradation of heparan sulfate and mucopolysaccharidoses resulting from the deficiency of individual enzymes. Some of these enzymes are also involved in the degradation of other glycosaminoglycans (not shown).
include enlarged, coarsely trabeculated diaphyses of the long bones with irregular metaphyses and epiphyses. With progression of the disease macrocephaly develops with thickened calvarium, premature closure of lambdoid and sagittal sutures, shallow orbits, enlarged J-shaped sella, and abnormal spacing of teeth with dentigerous cyst.

**Hurler-Scheie Disease**
The clinical phenotype of MPS-IH/S is intermediate between Hurler and Scheie diseases and is characterized by progressive somatic involvement, including dysostosis multiplex with little or no intellectual dysfunction. The onset of symptoms is usually observed between 3 and 8 yr of age; survival to adulthood is common. Cardiac involvement and upper airway obstruction contribute to clinical morbidity. Some patients have spondylolisthesis, which may cause cord compression.

**Scheie Disease**
MPS-IS is a comparatively mild disorder characterized by joint stiffness, aortic valve disease, corneal clouding, and mild dysostosis multiplex. Onset of significant symptoms is usually after the age of 5 yr, with diagnosis made between 10 and 20 yr of age. Patients with Scheie disease have normal intelligence and stature but have significant joint and ocular involvement. A carpal tunnel syndrome often develops. Ophthalmic features include corneal clouding, glaucoma, and retinal degeneration. Obstructive airway disease, causing sleep apnea, develops in some patients, necessitating tracheotomy. Aortic valve disease is common and has required valve replacement in some patients.

**Mucopolysaccharidosis II**
Hunter disease, (MPS-II) is an X-linked disorder caused by the deficiency of iduronate 2-sulfatase (IDS). The gene encoding IDS is mapped to Xq28. Point mutations of the IDS gene have been detected in approximately 80% of patients with MPS-II. Major deletions or rearrangements of the IDS gene have been found in the rest, and these are usually associated with a more severe clinical phenotype. As an X-linked recessive disorder, Hunter disease manifests almost exclusively in males. However, it has been observed in females and this is

---

**Table 88-1**
Recognition Pattern of Mucopolysaccharidoses

<table>
<thead>
<tr>
<th>MANIFESTATIONS</th>
<th>I-H</th>
<th>I-S</th>
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<th>III</th>
<th>IV</th>
<th>VI</th>
<th>VII</th>
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<tbody>
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<td>+</td>
<td>−</td>
<td>±</td>
<td>+</td>
<td>−</td>
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<td>Coarse facial features</td>
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<td>(+)</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>±</td>
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<tr>
<td>Corneal clouding</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>(−)</td>
<td>+</td>
<td>±</td>
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<tr>
<td>Visceromegaly</td>
<td>+</td>
<td>(+)</td>
<td>+</td>
<td>(+)</td>
<td>−</td>
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<td></td>
</tr>
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<td>Short stature</td>
<td>+</td>
<td>(+)</td>
<td>−</td>
<td>+</td>
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<td></td>
</tr>
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<td>(+)</td>
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</table>

I-H, Hurler disease; I-S, Scheie disease; II Hunter disease; III, Sanfilippo disease; IV, Morquio disease; VI, Maroteaux-Lamy disease; VII Sly disease.

**Figure 88-2** Patients with various types of mucopolysaccharidoses. MPS-I: Hurler disease, patient age 3 yr; MPS-II: Hunter disease, patient age 12 yr; MPS-III: Sanfilippo disease, patient age 4 yr; MPS-IV: Morquio disease, patient age 10 yr; MPS-VI: Maroteaux-Lamy disease, patient age 15 yr.
<table>
<thead>
<tr>
<th>MPS TYPE</th>
<th>EPONYM</th>
<th>INHERITANCE</th>
<th>GENE CHROMOSOME</th>
<th>MAIN CLINICAL FEATURES</th>
<th>DEFECTIVE ENZYME</th>
<th>ASSAY</th>
<th>MIM NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-H</td>
<td>Pfaunder-Hurler</td>
<td>AR</td>
<td>IDUA 4p16.3</td>
<td>Severe Hurler phenotype, mental deficiency, corneal clouding, death usually before age 14 yr, Hurler phenotype, mental retardation, corneal clouding, death usually before age 14 yr</td>
<td>α-L-iduronidase</td>
<td>L,F,Ac,CV</td>
<td>252800 607014</td>
</tr>
<tr>
<td>I-S</td>
<td>Scheie</td>
<td>AR</td>
<td>IDUA 4p16.4</td>
<td>Stiff joints, corneal clouding, aortic valve disease, normal intelligence, survive to adulthood</td>
<td>α-L-iduronidase</td>
<td>L,F,Ac,CV</td>
<td>607016</td>
</tr>
<tr>
<td>I-HS</td>
<td>Hurler-Scheie</td>
<td>AR</td>
<td>IDUA 4p16.4</td>
<td>Phenotype intermediate between I-H and I-S</td>
<td>α-L-iduronidase</td>
<td>L,F,Ac,Cv</td>
<td>607015</td>
</tr>
<tr>
<td>II</td>
<td>Hunter</td>
<td>XLR</td>
<td>IDS Xq27.3-28</td>
<td>Severe course similar to I-H but clear corneas. Mild course: less pronounced features, later manifestation, survival to adulthood with mild or without mental deficiency</td>
<td>Iduronate sulfatase</td>
<td>S,F,Ac,Cv</td>
<td>309900</td>
</tr>
<tr>
<td>III-A</td>
<td>Sanfilippo A</td>
<td>AR</td>
<td>SGSH 17q25.3</td>
<td>Behavioral problems, sleeping disorder, aggression, progressive dementia, mild dysmorphism, coarse hair, clear corneas; survival to adulthood possible</td>
<td>Heparan-S-sulfamidase</td>
<td>L,F,Ac,Cv</td>
<td>252900 605270</td>
</tr>
<tr>
<td>III-B</td>
<td>Sanfilippo B</td>
<td>AR</td>
<td>NAGLU 17q21</td>
<td></td>
<td>N-Acetyl-α-D-glucosaminidase</td>
<td>S,F,Ac,Cv</td>
<td>252920</td>
</tr>
<tr>
<td>III-C</td>
<td>Sanfilippo C</td>
<td>AR</td>
<td>HGSNAT 8p11.21</td>
<td></td>
<td>Acetyl-CoAα-glucosaminide</td>
<td>F,Ac</td>
<td>252930</td>
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<tr>
<td>III-D</td>
<td>Sanfilippo D</td>
<td>AR</td>
<td>GNS 12q14</td>
<td></td>
<td>N-acetyltransferase</td>
<td>F,Ac</td>
<td>252940 607664</td>
</tr>
<tr>
<td>IV-A</td>
<td>Morquio A</td>
<td>AR</td>
<td>GALNS 16q24.3</td>
<td>Short-trunk dwarfism, fine corneal opacities, characteristic bone dysplasia; final height below 125 cm</td>
<td>N-Acetyl-galactosamine-6-sulfatase</td>
<td>L,F,Ac</td>
<td>253000</td>
</tr>
<tr>
<td>IV-B</td>
<td>Morquio B</td>
<td>AR</td>
<td>GLB1 3p21.33</td>
<td>Same as IV-A, but milder; adult height over 120 cm</td>
<td>β-Galactosidase</td>
<td>L,F,Ac,Cv</td>
<td>253010 230500</td>
</tr>
<tr>
<td>VI</td>
<td>Maroteaux-Lamy</td>
<td>AR</td>
<td>ARSβ 5q11-q13</td>
<td>Hurler phenotype with marked corneal clouding but normal intelligence; mild, moderate and severe expression in different families</td>
<td>N-Acetyl-galactosamine-4-sulfatase (aryl sulfatase B)</td>
<td>L,F,Ac</td>
<td>253200</td>
</tr>
<tr>
<td>VII</td>
<td>Sly</td>
<td>AR</td>
<td>GUSB 7q21.11</td>
<td>Varying from fetal hydrops to mild dysmorphism; dense inclusions in granulocytes</td>
<td>β-Glucuronidase</td>
<td>S,F,Ac,Cv</td>
<td>253220</td>
</tr>
<tr>
<td>IX</td>
<td>Hyaluronidase deficiency</td>
<td>AR</td>
<td>HYAL1 3p21.3</td>
<td>Periarticular masses, no Hurler phenotype H</td>
<td>Hyaluronidase 1</td>
<td>S</td>
<td>601492</td>
</tr>
</tbody>
</table>

Ac, cultured amniotic cells; Af, amniotic fluid; Cv, chorionic villi; F, cultured fibroblasts; L, leukocytes; MIM, Mendelian Inheritance in Man Catalogue; S, serum.

explained by skewed inactivation of the X-chromosome carrying the normal gene.

Marked molecular heterogeneity explains the wide clinical spectrum of Hunter disease. Patients with severe MPS-II have features similar to those of Hunter disease except for the lack of corneal clouding and the somewhat slower progression of somatic and central nervous system (CNS) deterioration. Coarse facial features, short stature, dysostosis multiplex, joint stiffness, and intellectual disability manifest between 2 and 4 yr of age. Grouped skin papules are present in some patients. Extensive mongoloid spots present at birth have been observed in African and Asian patients and may be an early marker of the disease. Gastrointestinal storage may produce chronic diarrhea. Communicating hydrocephalus and spastic paraplegia may develop due to thickened meninges. In severely affected patients, extensive, slowly progressive neurologic involvement precedes death, which usually occurs between 10 and 15 yr of age.

Patients with the mild form can have a near-normal or normal life span, minimal CNS involvement and slow progression of somatic deterioration with preservation of cognitive function in adult life. Survival to ages 65 and 87 yr has been reported and some patients have had children. Somatic features are Hurler-like but milder with a greatly reduced rate of progression. Adult height may exceed 150 cm. Airway involvement, valvular cardiac disease, hearing impairment, carpal tunnel syndrome, and joint stiffness are common and can result in significant loss of function in both the mild and severe forms.
Mucopolysaccharidoses III

Sanfilippo disease makes up a genetically heterogeneous but clinically similar group of 4 recognized types. Each type is caused by a different enzyme deficiency involved in the degradation of heparan sulfate (see Fig. 88-1). Mutations have been found in all the MPS-III disorders for which the genes have been isolated.

Phenotypic variation exists in MPS-III patients, but to a lesser degree than in other MPS disorders. Patients with Sanfilippo disease are characterized by slowly progressive, severe CNS involvement with mild somatic disease. Such disproportionate involvement of the CNS is unique to MPS-III. Onset of clinical features usually occurs between 2 and 6 yr in a child who previously appeared normal. Presenting features include delayed development, hyperactivity with aggressive behavior, coarse hair, hirsutism, sleep disorders, and mild hepatosplenomegaly. Delays in diagnosis of MPS-III are common because of the mild physical features, hyperactivity, and slowly progressive neurologic disease. Severe neurologic deterioration occurs in most patients by 6-10 yr, accompanied by rapid deterioration of social and adaptive
skills. Severe behavior problems such as sleep disturbance, uncontrolled hyperactivity, temper tantrums, destructive behavior, and physical aggression are common. Profound developmental regression and behavior problems often occur in patients with normal physical strength, making management particularly difficult.

**Mucopolysaccharidosis IV**

Morquio disease (MPS-IV) is caused by a deficiency of N-acetylgalactosamin-6-sulfatase (MPS-IVA) or of β-galactosidase (MPS-IVB). Both result in the defective degradation of keratan sulfate. The gene encoding N-acetylgalactosamin-6-sulfatase is on chromosome 16q24.3 and the gene encoding β-galactosidase, GLB1, on chromosome 3p21.33. β-Galactosidase catalyzes hydrolysis of GM1 ganglioside in addition to endohydrolisis of keratan sulfate, and most mutations of GLB1 result in generalized gangliosidosis, a spectrum of neurodegenerative disorders associated with dysostosis multiplex. A W273L mutation of the GLB1 gene, either in the homozygous state or as part of compound heterozygosity, commonly results in Morquio B disease.

Both types of Morquio disease are characterized by short-trunk dwarfism, fine corneal deposits, a skeletal dysplasia that is distinct from other mucopolysaccharidoses, and preservation of intelligence. MPS-IVA is usually more severe than MPS-IVB with adult heights of less than 125 cm in the former and more than 150 cm in the latter. However, there is considerable variability of expression in both subtypes. The appearance of genua valga, kyphosis, growth retardation with short trunk and neck, and waddling gait with a tendency to fall are early symptoms of MPS-IV. Extraskeletal manifestations include mild corneal clouding, small teeth with abnormally thin enamel, frequent cavities formation and occasionally hepatomegaly and cardiac valvular lesions. Instability of the odontoid process and ligamentous laxity is regularly present and can result in life-threatening atlantoaxial instability and dislocation. Surgery to stabilize the upper cervical spine, usually by posterior spinal fusion, before the development of cervical myelopathy can be lifesaving.

**Mucopolysaccharidosis VI**

Maroteaux-Lamy disease is caused by mutations of the ARSB gene on chromosome 5q11.13 encoding N-acetylgalactosamine-4-sulfatase (aryl sulfatase B). It is characterized by severe to mild somatic involvement, as seen in MPS-I, but with preservation of intelligence. The somatic involvement of the severe form of MPS-IV is characterized by corneal clouding, coarse facial features, joint stiffness, valvular heart disease, communicating hydrocephalus, and dysostosis multiplex. In the severe form, growth can be normal for the first few years of life but seems to virtually stop after age 6-8 yr. The mild to intermediate forms of Maroteaux-Lamy disease can be easily confused with Scheie syndrome. Spinal cord compression from thickening of the dura in the upper cervical canal with resultant myelopathy is a frequent occurrence in patients with MPS-VI.

**Mucopolysaccharidosis VII**

Sly syndrome (MPS-VII) is caused by mutations of the GUSB gene located on chromosome 7q21.11. Mutations result in a deficiency of β-glucuronidase, intracellular storage of glycosaminoglycan fragments and a very wide range of clinical involvement. The most severe form presents as lethal nonimmune fetal hydrops and may be detected in utero by ultrasound. Some severely affected newborns survive for some months and have, or develop, signs of lysosomal storage including thick skin, visceralomegaly, and dysostosis multiplex. Less-severe forms of MPS-VII present during the first years of life with features of MPS-I but slower progression. Corneal clouding varies. Patients with manifestation after 4 yr of life have skeletal abnormalities of dysostosis multiplex but normal intelligence and usually clear cornea. They may be found incidentally on the basis of a blood smear that shows coarse granulocytic inclusions.

**Mucopolysaccharidosis IX**

The disorder is caused by a mutation in the HYAL1 gene on chromosome 3p21.2-21.2 encoding one of 3 hyaluronidases. Clinical findings in the only known patient, a 14-year old girl, were bilateral nodular soft-tissue periarticular masses, lysosomal storage of GAGs in histio- cytes, mildly dysorphic craniofacial features, short stature, normal joint movement and normal intelligence. Small erosions in both acetabula were the only radiographic findings.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**

Clinical suspicion of a MPS justifies a skeletal survey. Radiographs of chest, spine, pelvis and hands may show early signs of dysostosis multiplex. The next diagnostic step is to assay the urinary excretion of GAG. Semiquantitative spot tests are quick and inexpensive but subject to both false-positive and false-negative results. Quantitative analysis of single GAG by various methods, or of oligosaccharides by tandem mass spectrometry, is preferable and reveals type-specific profiles. Morquio disease is often missed in urinary assays but can reliably be diagnosed in serum using monoclonal antibodies to keratan sulfate.

Any individual who is suspected of an MPS disorder based on clinical features, radiographic results, or urinary GAG screening tests should have a definitive diagnosis established by enzyme assay. Serum, leukocytes, or cultured fibroblasts are used as the tissue source for measuring lysosomal enzymes (see Table 88-2).

Prenatal diagnosis is available for all MPSs and is carried out on cultured cells from amniotic fluid or chorionic villus biopsy. Measurement of GAGs in amniotic fluid is unreliable. Carrier testing in Hunter syndrome, an X-linked disorder, requires analysis of IDS gene once the specific mutation or chromosome arrangement in the family under consideration is known. Prenatal molecular analysis must be offered in a male fetus of a proven female carrier of the IDS gene. His risk to be affected is 50%. It is very small, but not zero, in a female fetus as a result of skewed maternal X-chromosome inactivation. Molecular analysis in patients with other enzymatically proven mucopolysaccharidoses or in known carriers is costly and usually not required. MPSs I, II, and VI are candidates for neonatal blood spot screening by tandem mass spectrometry allowing early diagnosis and enzyme replacement therapy.

Mucolipidoses and oligosaccharidoses manifest with the same clinical and radiographic features as mucopolysaccharidoses. In these conditions the urinary excretion of GAGs is not elevated. Hurler-like facial features, joint contractures, dysostosis multiplex and elevated urinary GAG excretion differentiate the mucopolysaccharidoses from congenital disorders of glycosylation and other neurodegenerative and dwarfing conditions.

**TREATMENT**

Hematopoietic stem cell transplantation and enzyme replacement therapy are performed in specialized institutions (Table 88-3). Experimental forms of therapy include substrate reduction by flavonoids, gene silencing, read-through attempts and transplantation of autolo- gous hematopoietic stem cells that have been genetically modified ex vivo to express the missing protein. Symptomatic measures are listed in Table 88-4.

Bone marrow transplantation from related or unrelated donors and cord blood transplantation have resulted in significant clinical improvement of somatic disease in MPSs I, II, and VI. Clinical effects are increased life expectancy, resolution or improvement of growth, hepatosplenomegaly, joint stiffness, facial appearance, pebbly skin changes in MPS-II, obstructive sleep apnea, heart disease, communicating hydrocephalus, and hearing loss. Enzyme activity in serum and urinary GAG excretion normalize. Transplantation does not significantly improve the neuropsychologic outcome of MPS patients with impaired cognition at the time of transplantation. This is true for MPSs IH, II, and III. However, patients with MPS-I who have undergone transplantation before 24 mo of age and with a baseline mental development index greater than 70 have improved long-term outcome. Early transplantation in MPS-II may have the same effect. Transplantation in MPS-VI stabilizes or improves cardiac manifestations, posture and joint mobility. Stem cell transplantation does not correct skeletal and ocular anomalies and they have to be treated with appropriate orthopedic and ophthalmologic procedures. Cord blood
transplantation is the therapy of choice in children with MPS-IH, and possibly MPS-II, before the age of 2 yr, but transplantation-related death or primary graft failure, which occur in approximately one-third of the patients, must be weighed against other therapeutic options.

**Enzyme replacement** using recombinant α-L-iduronidase has been approved for patients with MPS-I. It reduces organomegaly and ameliorates rate of growth, joint mobility, reduces the number of episodes of sleep apnea and urinary GAG excretion. The enzyme does not cross the blood–brain barrier and does not prevent deterioration of cognition and other neurologic functions. Consequently, this therapy is reserved for patients with mild CNS involvement. To stabilize extraneural manifestations, it is also recommended in young patients before stem cell transplantation. Recombinant iduronate-2-sulfatase ameliorates the nonneurologic manifestations of Hunter disease, and recombinant N-acetylgalactosamine-4-sulfatase has been successfully tested in patients with MPS-VI.

Primary prevention through genetic counseling and tertiary prevention to avoid or arrest complications remain the mainstay of pediatric care. Multidisciplinary attention to respiratory and cardiovascular complications, hearing loss, carpal tunnel syndrome, spinal cord compression, hydrocephalus and other problems can greatly improve the quality of life for patients and their families (see Table 88-4). The progressive nature of clinical involvement in MPS patients dictates the need for specialized and coordinated evaluation.

**Bibliography is available at Expert Consult.**
Bibliography


Chapter 89
Disorders of Purine and Pyrimidine Metabolism
James C. Harris

The inherited disorders of purine and pyrimidine metabolism cover a broad spectrum of illnesses with various presentations. These include hyperuricemia, acute renal failure, renal stones, gout, unexplained neurologic deficits (seizures, muscle weakness, choreoathetoid and dystonic movements), developmental disability, intellectual disability, compulsive self-injury and aggression, autistica-like behavior, unexplained anemia, failure to thrive, susceptibility to recurrent infection (immune deficiency), and deafness. When identified, all family members should be screened.

Purines and pyrimidines form the basis of nucleotides and nucleic acids (DNA and RNA) and so are involved in all biologic processes. Metabolically active nucleotides are formed from heterocyclic nitrogen-containing purine bases (guanine and adenine) and pyrimidine bases (cytosine, uridine, and thymine); all cells require a balanced supply of nucleotides for growth and survival. Purines provide the primary source of cellular energy through adenosine triphosphate (ATP) and the basic coenzymes (nicotinamide adenine dinucleotide and its reduced form) for metabolic regulation and play a major role in signal transduction (guanosine triphosphate [GTP], cyclic adenosine monophosphate, cyclic guanosine monophosphate). Figure 89-1 shows the early steps in the biosynthesis of the purine ring. Purines are primarily produced from endogenous sources, and in the usual circumstances dietary purines have a small role. The end product of purine metabolism in humans is uric acid (2,6,8-trioxypurine).

Uric acid is not a specific disease marker so the cause of its elevation must be determined. The serum level of uric acid present at any time depends on the size of the purine nucleotide pool which is derived from de novo purine synthesis, catabolism of tissue nucleic acids, and increased turnover of preformed purines. Uric acid is poorly soluble and must be excreted continuously to avoid toxic accumulation in the body. Its renal excretion involves the following components: (1) glomerular filtration, (2) reabsorption in the proximal convoluted tubule, (3) secretion near the terminus of the proximal tubule, and (4) limited reabsorption near these secretory sites. Thus, renal loss of uric acid is a result of renal tube excretion and is a function of serum uric acid concentration and non-specific transporters that remove uric acid. Because renal tubule excretion is greater in children than in adults, serum uric acid levels are a less reliable indicator of uric acid production in children than in adults, and, consequently, measurement of the level in urine may be required to determine excessive production. Clearance of a smaller portion of uric acid is via the gastrointestinal tract (biliary and intestinal secretion). Owing to poor solubility of uric acid under normal circumstances, uric acid is near the maximal tolerable limits, and small alterations in production or solubility or changes in secretion may lead to hyperuricemia and can result in precipitation in extremities such as fingers or toes, which defines clinical gout. In renal insufficiency, urate excretion is increased by residual nephrons and by the gastrointestinal tract. Increased production of uric acid is found in malignancy, Reye syndrome, Down syndrome, psoriasis, sickle cell anemia, cyanotic congenital heart disease, pancreatic enzyme replacement, glycogen storage disease types I, III, IV, and V, hereditary fructose intolerance, and acyl-coenzyme A dehydrogenase deficiency.

The metabolism of both purines and pyrimidines can be divided into biosynthetic, salvage and catabolic pathways. The first, the de novo pathway, involves a multistep biosynthesis of phosphorylated ring structures from precursors such as CO2, glycine, and glutamine. Purine and pyrimidine nucleotides are produced from ribose-5-phosphate or carbamyl phosphate, respectively. The second, a single-step salvage pathway, recovers purine bases and pyrimidine nucleosides derived from either dietary intake or the catabolic pathway (Figs. 89-2 and 89-3). In the de novo pathway, the nucleosides guanosine, adenosine, cytidine, uridine, and thymidine are formed by the addition of ribose-1-phosphate to the purine bases guanine or adenine, and to the pyrimidine bases cytosine, uracil, and thymine respectively. The phosphorylation of these nucleosides produces monophosphate, diphosphate, and triphosphate nucleotides, as well as the deoxy-nucleotides that are utilized for DNA formation. Under usual circumstances, the salvage pathway predominates over the biosynthetic pathway, as nucleotide salvage saves energy for cells. Only a small fraction of the nucleotides turned over by the body each day are degraded and excreted.

Synthesis of nucleotides is most active in tissues with high rates of cellular turnover, such as gut epithelium, skin, and bone marrow. The third pathway is catabolism. The end product of the catabolic pathway of the purines in humans is uric acid, whereas catabolism of pyrimidines produces citric acid cycle intermediates.

Inborn errors in the synthesis of purine nucleotides comprise the phosphoribosylpyrophosphate synthetase spectrum of disorders, including deficiency and superactivity, adenylosuccinate lyase deficiency, and 5-amino-4-imizolecarboxamide (AICA) riboside deficiency (AICARibosiduria). Disorders resulting from abnormalities in purine catabolism comprise muscle adenosine monophosphate (AMP) deaminase deficiency, adenosine deaminase deficiency, purine nucleoside phosphorylase deficiency, and xanthine oxidoreductase deficiency. Disorders resulting from the purine salvage pathway comprise hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency, and adenosine phosphoribosyltransferase (APRT) deficiency.

The sole inborn error of pyrimidine synthesis is hereditary orotic aciduria (uridine monophosphate synthase deficiency). Disorders resulting from abnormalities in pyrimidine catabolism comprise dihydropyrimidine dehydrogenase (DPD) deficiency, dihydropyrimidinase (DPH) deficiency, and β-ureidopropionase deficiency, pyrimidine 5′-nucleotidase deficiency, and mitochondrial thymidine phosphorylase deficiency. A disorder resulting from the pyrimidine salvage is thymidine kinase 2 deficiency.

GOUT
Gout presents with hyperuricemia, uric acid nephrolithiasis, and acute inflammatory arthritis. Gouty arthritis is caused by monosodium urate crystal deposits that result in inflammation in joints and surrounding tissues. The presentation is most commonly monoarticular, typically in the metatarsophalangeal joint of the big toe. Tophi, deposits of monosodium urate crystals, may occur over points of insertion on the elbows, knees, and feet or over the helix of the ears. Primary gout Ordinarily occurs in middle-aged men, results mainly from decreased renal excretion of uric acid, or purine overconsumption, or high intake of alcohol or fructose, or a combination of these factors. Gout occurs in any condition that leads to reduced clearance of uric acid: during therapy for malignancy or with dehydration, lactic acidosis, ketoacidosis, starvation, diuretic therapy, and renal failure. Excessive purine, alcohol, or fructose ingestion may increase uric acid levels. The biochemical etiology of gout is unknown for most of those affected, and it is considered to be a polygenic trait. Purine overproduction is a rare cause of primary gout, and is associated with several genetic disorders discussed below. Secondary gout is either the result of another disorder in which there is rapid tissue breakdown or cellular turnover leading to increased production or decreased excretion of uric acid, or the result of some types of drug treatment, for example diuretics cause plasma volume reduction and can precipitate a gouty attack.

Gout resulting from endogenous purine overproduction is associated with hereditary disorders of 3 different enzymes that result in
Juvenile gout resulting from purine underexcretion is polygenic, consisting of the familial juvenile hyperuricemic nephropathy group of disorders. This includes medullary cystic kidney disease type 2, mapped to chromosome 16p11.2, which has been shown to result from uromodulin mutations; the term uromodulin-associated kidney disease has been proposed for them. Other genes classified as forms of familial juvenile hyperuricemic nephropathy include those for renin and hepatic nuclear factor-1β. Unlike the 3 inherited purine disorders that are X-linked and the recessively inherited glycogen storage disease, these are autosomal dominant conditions. Familial juvenile hyperuricemic nephropathy is associated with severe renal hypoexcretion of hyperuricemia. These comprise the HPRT deficiency spectrum (ranging from severe deficiency or Lesch-Nyhan syndrome to partial HPRT deficiency), 2 forms of superactivity of PP-ribose-P synthetase, and glycogen storage disease type I (glucose-6-phosphatase deficiency; see Chapter 87.1). In the first two, the basis of hyperuricemia is purine nucleotide and uric acid overproduction, whereas in the third it is both excessive uric acid production and diminished renal excretion of urate. Glycogen storage disease types III, V, and VII are associated with exercise-induced hyperuricemia, the consequence of rapid ATP utilization and failure to regenerate it effectively during exercise (see Chapter 87.1).
uric acid. Although it most commonly presents from puberty up to the 3rd decade, it has been reported in infancy. It is characterized by early onset, hyperuricemia, gout, familial renal disease, and low urate clearance relative to glomerular filtration rate. It occurs in both males and females and is frequently associated with a rapid decline in renal function that may lead to death unless diagnosed and treated early. Once familial juvenile hyperuricemic nephropathy is recognized, presymptomatic detection is of critical importance to identify asymptomatic family members with hyperuricemia and to begin treatment, when indicated, to prevent nephropathy.

**Genetics**

Familial juvenile hyperuricemic nephropathy-2 (HNFJ2; 613092) is caused by mutation in the renin gene (REN; 179820) on chromosome 1q32. HNFJ3 (614227) has been mapped to chromosome 2p22.1-p21.

**Treatment**

Treatment of hyperuricemia involves the combination of allopurinol or febuxostat (xanthine oxidase inhibitors) to decrease uric acid production, probenecid to increase uric acid clearance in those with normal renal function, and increased fluid intake to reduce the concentration of uric acid. A low purine diet, weight reduction, and reduced alcohol and reduced fructose intake (as fructose both reduces urate clearance and accelerates ATP breakdown to uric acid) are recommended.

### ABNORMALITIES IN PURINE SALVAGE

#### HPRT Deficiency

Lesch-Nyhan disease (LND) is a rare X-linked disorder of purine metabolism that results from HPRT deficiency. This enzyme is normally present in each cell in the body, but its highest concentration is in the brain, especially in the basal ganglia. Clinical manifestations include hyperuricemia, intellectual disability, dystonic movement disorder that may be accompanied by choreoathetosis and spasticity, dysarthric speech, and compulsive self-biting, usually beginning with the eruption of teeth.

There is a severity spectrum for the clinical presentations of HPRT deficiency. HPRT levels are related to the extent of motor symptoms, to the presence or absence of self-injury, and possibly to the level of cognitive function. Purine overproduction is present. The majority of individuals with classic LND have low or undetectable levels of the HPRT enzyme. Partial deficiency in HPRT (Kelley-Seegmiller syndrome) with more than 1.5-2.0% enzyme is associated with purine overproduction and variable neurologic dysfunction (neurologic HPRT deficiency). HPRT deficiency with activity levels of normal still exhibit purine (and uric acid) overproduction but apparently normal cerebral functioning (HPRT-related hyperuricemia) although cognitive deficits may occur. Qualitatively similar cognitive deficit profiles have been reported in both LND and variant cases. Variants produced scores that are intermediate between those of patients with LND and normal controls on nearly every neuropsychological measure tested.

**Genetics**

The HPRT gene has been localized to the long arm of the X chromosome (q26-q27). The complete amino acid sequence for HPRT is known (approximately 44 kb; 9 exons). The disorder appears in males; occurrence in females is extremely rare and ascribed to nonrandom inactivation of the normal X chromosome. Absence of HPRT activity prevents the normal metabolism of hypoxanthine resulting in excessive uric acid production and manifestations of gout, necessitating specific drug treatment (allopurinol). Because of the enzyme deficiency, hypoxanthine accumulates in the cerebrospinal fluid, but uric acid does not; uric acid is not produced in the brain and does not cross the blood–brain barrier. The behavior disorder is not caused by hyperuricemia or excess hypoxanthine because patients with partial HPRT deficiency, the variants with hyperuricemia, do not self-injure and infants having isolated hyperuricemia from birth do not develop self-injurious behavior.

The prevalence of the classic LND has been estimated at 1 in 100,000 to 1 in 380,000 persons based on the number of known cases in the United States. The incidence of partial variants is not known. Those with the classic syndrome rarely survive the 3rd decade because of renal or respiratory compromise. The life span may be normal for patients with partial HPRT deficiency without severe renal involvement.

**Pathology**

No specific brain abnormality is documented after detailed histopathology and electron microscopy of affected brain regions. Magnetic resonance imaging has documented reductions in the volume of basal ganglia nuclei. Abnormalities in neurotransmitter metabolism have been identified in 3 autopsied cases. All 3 patients had very low HPRT levels (less than 1% in striatal tissue and 1-2% of control in thalamus cortex). There was a functional loss of 65-90% of the nigrostriatal and...
Disorders of Purine and Pyrimidine Metabolism

mesolimbic dopamine terminals, although the cells of origin in the substantia nigra did not show dopamine reduction. The brain regions primarily involved were the caudate nucleus, putamen, and nucleus accumbens. It is proposed that the neurochemical changes may be linked to functional abnormalities, possibly resulting from a diminution of arborization or branching of dendrites rather than cell loss. A neurotransmitter abnormality is demonstrated by changes in cerebrospinal fluid neurotransmitters and their metabolites, and confirmed by positron emission tomography scans of dopamine function. Reductions in vivo in the presynaptic dopamine transporter have been documented in the caudate and putamen of 6 individuals.

The mechanism whereby HPRT leads to the neurologic and behavioral symptoms is unknown. However, both hypoxanthine and guanine metabolism are affected and GTP and adenosine have substantial effects on neural tissues. The functional link between purine nucleotides and the dopamine system is through salvage of guanine by HPRT to form GTP: this is essential for GTP cyclohydrolase activity, the first step in the synthesis of pterins and dopamine. Patients with inherited GTP cyclohydrolase deficiency show clinical features in common with LND. Dopamine reduction in brain is documented in HPRT-deficient strains of mutant mice. Dopamine binding to its receptor results in either an activation (D1 receptor) or an inhibition (D2 receptor) of adenylcyclase. Both receptor effects are mediated by G proteins (GTP-binding proteins) dependent on guanine diphosphate in the guanine diphosphate/GTP exchange for cellular activation. Dopamine and adenosine systems are also linked through the role of adenosine as a neuroprotective agent in preventing neurotoxicity. Adenosine derives from AMP which depends on hypoxanthine salvage in the brain by HPRT. Adenosine agonists mimic the biochemical and behavioral actions of dopamine antagonists, whereas adenosine receptor antagonists act as functional dopamine agonists. LND can thus be seen as arising ultimately from nucleotide depletion specifically in the brain, which relies upon the HPRT salvage pathway, leading to dopamine and adenosine depletions.

Clinical Manifestations

At birth, infants with LND have no apparent neurologic dysfunction. After several months, developmental delay, intellectual disability and neurologic signs become apparent. Before the age of 4 mo, hypotonia, recurrent vomiting, and difficulty with secretions may be noted. By approximately 8-12 mo, extrapyramidal signs appear, primarily dystonic movements. In some cases, spasticity may become apparent at this time; in some instances, it becomes apparent later in life.

Cognitive function is usually reported to be in the mild-to-moderate range of intellectual disability, although some individuals test in the low normal range. Because test scores may be influenced by difficulty in testing the subjects owing to their movement disorder and dysarthric speech, overall intelligence may be underestimated.

The age of onset of self-injury may be as early as 1 yr and occasionally as late as the teens. Self-injury occurs, although all sensory modalities, including pain, are intact. The self-injurious behavior usually begins with self-biting, although other patterns of self-injurious behavior emerge with time. Most characteristically, the fingers, mouth, and buccal mucosa are mutilated. Self-biting is intense and causes tissue damage and may result in the amputation of fingers and substantial loss of tissue around the lips. Extraction of primary teeth may be required. The biting pattern can be asymmetric, with preferential mutilation of the left or right side of the body. The type of behavior is different from that seen in other intellectual disability syndromes involving self-injury. Self-hitting and head-banging are the most common initial presentations in other syndromes. The intensity of the self-injurious behavior generally requires that the patient be restrained. When restraints are removed, the patient with LND may appear terriified, and stereotypically place a finger in the mouth. The patient may ask for restraints to prevent elbow movement; when the restraints are placed or replaced, he may appear relaxed and more good-humored. Dysarthric speech may cause interpersonal communication problems; however, the higher-functioning children can express themselves fully and participate in verbal therapy.

The self-mutilation presents as a compulsive behavior that the child tries to control but frequently is unable to resist. Older individuals may enlist the help of others and notify them when they are comfortable enough to have restraints removed. In some instances, the behavior may lead to deliberate self-harm. The LND individual may also show compulsive aggression and inflict injury to others through pinching, grabbing, or hitting or by using verbal forms of aggression. Afterward he may apologize, stating that this behavior was out of his control. Other maladaptive behaviors include head- or limb-banging, eye-poking, and psychogenic vomiting.

Diagnosis

The presence of dystonia along with self-mutilation of the mouth and fingers suggests LND. With partial HPRT deficiency, recognition is linked to either hyperuricemia alone or hyperuricemia and a dystonic movement disorder. Serum levels of uric acid that exceed 4-5 mg uric acid/DL and a urine uric acid:creatinine ratio of 3:4-1 are highly suggestive of HPRT deficiency, particularly when associated with neurologic symptoms. The definitive diagnosis requires an analysis of the HPRT enzyme. This is assayed in an erythrocyte lysate. Individuals with classic LND have near 0% enzyme activity and those with partial variants show values between 1.5% and 60%. The intact cell HPRT assay in skin fibroblasts offers a good correlation between enzyme activity and the severity of the disease. Molecular techniques are used for gene sequencing and the identification of carriers.

Differential diagnosis includes other causes of infantile hypotonia and dystonia. Children with LND are often initially incorrectly diagnosed as having athetoid cerebral palsy. When a diagnosis of cerebral palsy is suspected in an infant with a normal prenatal, perinatal, and postnatal course, then LND should be considered. Partial HPRT deficiency may be associated with acute renal failure in infancy; therefore, clinical awareness of partial HPRT deficiency is of particular importance. The simplest test to exclude LND or partial deficiency is the urinary uric acid:creatinine ratio.

An understanding of the molecular disorder has led to effective drug treatment for uric acid accumulation and arthritic tophi, renal stones, and neuropathy. However, reduction in uric acid alone does not influence the neurologic and behavioral aspects of LND. Despite treatment from birth for uric acid elevation, behavioral and neurologic symptoms are unaffected. The most significant complications of LND are renal failure and self-mutilation.

Treatment

Medical management of this disorder focuses on the prevention of renal failure by pharmacologic treatment of hyperuricemia with high fluid intake along with alkalinization and allopurinol (or more febuxostat). A low purine diet and reduced fructose intake are desirable. Allopurinol treatment must be monitored because urinary oxypurine excretion with all overproduction disorders is sensitive to allopurinol, resulting in an increased urine concentration of xanthine, which is extremely insoluble. Self-mutilation is reduced through behavior management, and the use of restraints or removal of teeth or both. Pharmacologic approaches to decrease anxiety and spasticity with medication have mixed results. Drug therapy focuses on symptomatic management of anticipatory anxiety, mood stabilization and reduction of self-injurious behavior. Although there is no standard drug treatment, diazepam may be helpful for anxiety symptoms, Risperdal for aggressive behavior and carbamazepine or gabapentin for mood stabilization. Each of these medications may reduce self-injurious behavior by helping to reduce anxiety and stabilize mood. 3-adenosylmethionine (SAMe), which is thought to act by countering nucleotide depletion in the brain, has been reported to specifically reduce the rate of self-injury in some cases.

Bone marrow transplantation, based on the hypothesis that the central nervous system damage is produced by a circulating toxin, has been carried out in several patients. Several infant patients have died of complications of bone marrow transplantation. To date, there is no evidence that bone marrow transplantation is a beneficial treatment...
Adenine Phosphoribosyltransferase Deficiency (Dihydroxyadeninuria)

Adenine phosphoribosyltransferase (APRT), a purine salvage enzyme, catalyzes the synthesis of AMP from adenine and 5-phosphoribosyl-1-pyrophosphate (PP-ribose-P). The absence of this enzyme results in the cellular accumulation of adenine and its being oxidized as 1-pyrophosphate (PP-ribose-P). The absence of this enzyme results in the cellular accumulation of adenine and its being oxidized as 1-pyrophosphate (PP-ribose-P). APRT deficiency is present from birth, becoming apparent as early as 5 mo and as late as the 7th decade.

Genetics

The disorder is an autosomal recessive trait with considerable clinical heterogeneity. The APRT gene is located on chromosome 16q (16q24.3) and encompasses 2.8 kb of genomic DNA.

Clinical Manifestations

Clinical manifestations include urinary calculus formation with crystalluria, urinary tract infections, hematuria, renal colic, dysuria and acute renal failure. The presence of brownish spots on the infant's diaper or of yellow-brown crystals in the urine is suggestive of the diagnosis. The 2,8-dihydroxyadenine is cleared efficiently by the kidneys and so does not accumulate in plasma, but precipitates readily in the renal lumen.

Laboratory

Urinary levels of adenine, 8-hydroxyadenine, and 2,8-dihydroxyadenine are elevated while plasma uric acid is normal. The deficiency may be complete (type I) or partial (type II); the partial deficiency is reported in Japan. The diagnosis is made based on the level of residual enzyme in erythrocyte lysates. The renal calculi, composed of 2,8-dihydroxyadenine, are radiolucent, soft, and easily crushed. These stones are not distinguishable from uric acid stones by routine tests but require high-performance liquid chromatography, UV, infrared, mass spectrometry, x-ray crystallography, or capillary electrophoresis for diagnosis, particularly to distinguish from stones in HPRT deficiency.

Treatment

Treatment includes high fluid intake, dietary purine restriction, and allopurinol, which inhibits the conversion of adenine to its metabolites, further 2,8-dihydroxyadenine excretion, and further stone formation. Alkalization of the urine is to be avoided, because, unlike that of uric acid, the solubility of 2,8-dihydroxyadenine does not increase up to pH 9. Shockwave lithotripsy has been reported to be successful. The prognosis depends on renal function at the time of diagnosis. Early treatment is critical in the prevention of stones because severe renal insufficiency may accompany late recognition.

DISORDERS LINKED TO PURINE NUCLEOTIDE SYNTHESIS

Phosphoribosylpyrophosphate Synthetase Superactivity and Deficiency

Phosphoribosylpyrophosphate (PRPP) is a substrate involved in the synthesis of essentially all nucleotides and important in the regulation of the de novo pathways of purine and pyrimidine nucleotide synthesis. The synthetase enzyme (PRPS) produces PRPP from ribose-5-phosphate and ATP, as shown in Figures 89-1 and 89-2. PRPP is the first intermediary compound in the de novo synthesis of purine nucleotides that lead to the formation of inosine monophosphate, then to ATP and GTP.

Genetic disorders of this enzyme affect only the PRPS-1 isoform; PRPS-2 mutations have not been described. PRPS-1 disorders are all X-linked and are divided into “superactivity,” which occurs as 2 phenotypes (infantile or early-childhood onset, and a milder form with late-juvenile or early-adult onset), and “deficiency,” which is a spectrum disorder that is distinguished clinically according to severity as 3 disorders: Arts syndrome, Charcot-Marie-Tooth disease X-linked-5, and X-linked deafness-2 (DFN2).

Superactivity of the enzyme results in an increased generation of PRPP in dividing cells. Because PRPP aminotransferase, the first enzyme of the purine de novo pathway, is not physiologically saturated by PRPP, the synthesis of purine nucleotides increases, and, consequently, the production of uric acid is increased. PRPP synthetase superactivity is one of the few hereditary disorders in which there is enhancement of the activity of an enzyme. The infantile or early-childhood form of PRPS-1 superactivity has severe neurologic attributes accompanied by uric acid overproduction, whereas individuals with the late-juvenile or early-adult presentation are neurologically normal but still have uric acid overproduction.

Deficiency of PRPS-1 produces depleted purine nucleotide synthesis in tissues dependent upon PRPS-1, which includes brain as well as other neural tissues and lung.

Genetics

Three distinct complementary DNAs for PRPS have been cloned and sequenced. Two forms, PRPS-1 and PRPS-2, are X-linked to Xq22-q24 and Xp22.2-p.22.3 (escapes X inactivation), respectively, and are widely expressed; the third locus maps to human chromosome 7 and appears to be transcribed only in the testes. PRPS-1 defects are thus inherited as X-linked traits and present with varying degrees of severity. The late-onset form of superactivity arises from increased transcription of normal messenger RNA; the cause of this has not been discovered. The early-onset form of superactivity arises from mutations affecting allosteric regulation of the protein that controls feedback inhibition by inorganic phosphate and dinucleotides. At the same time, these mutations destabilize the protein, so that in slow or nonreplicating cells, such as neurons and red blood cells, the enzyme becomes inactive. In contrast, the deficiency phenotypes of PRPS-1 are produced by mutations directly affecting enzyme function, usually in the substrate.
binding site. Even though the defect is X-linked it should be considered in a child or young adult of either sex with hyperuricemia and/or hyperuricosuria and normal HPRT activity in lysed red cells.

**Clinical Manifestations**
Clinical manifestations in affected hemizygous males with the early-onset form of superactivity include signs of uric acid overproduction that are apparent in infancy or early childhood and neurodevelopmental retardation and sensorineural deafness. Hypotonia, delays in motor milestones, ataxia, and autistic-like behavior have been described. Heterozygous female carriers may also develop gout and hearing impairment. The late-onset type is found in males who show only hyperuricemia and hyperuricosuria, but no neurologic signs. The mildest form of PRPS-1 deficiency manifests as progressive postlingual hearing loss in X-linked deafness-2. More severe mutations constitute the Charcot-Marie-Tooth disease X-linked-5 phenotype, which includes peripheral neuropathy, hearing impairment, and optic atrophy. The most severe PRPS-1 mutations occur in patients with Arts syndrome who also have central neuropathy and an impaired immune system. Females appear to be unaffected, but hemizygous males have usually not survived beyond the 1st decade, typically succumbing to lung disease. Therapy with S-adenosylmethionine has prolonged survival, although the neurologic deficits, including the deafness, do not appear to be responsive.

A mechanism for the neurologic symptoms is unknown but it can be hypothesized that nucleotide depletion is present in neural tissues including the brain. Abnormalities of hearing and vision are typical of PRPS-1 deficiency, where the absence of this enzyme presumably compromises these highly energy-dependent neural functions. The high transcript level of PRPS-1 in lung and bone marrow also suggests that its absence may be causal for the recurrent lung infections that characterize Arts syndrome.

**Laboratory**
For PRPS-1 “superactivity” (both juvenile and adult presentations), serum uric acid may be grossly raised and the urinary excretion of uric acid increased. For PRPS “deficiency,” uric acid is normal, not low, probably because PRPS-2 provides the major uric acid forming activity in liver and other major organs. Diagnosis requires that PRPS-1 activity be measured in erythrocytes and cultured fibroblasts. The adult superactivity disorder must be differentiated from partial HPRT deficiency involving the salvage pathway, which also presents with mild or absent neurologic traits accompanied by hyperuricemia.

**Treatment**
Treatment of PRPS deficiency, specifically Arts syndrome, has involved mainly experimental therapy with S-adenosylmethionine, as a dietary supplement to correct the depletion of purines. Dietary purines are usually not absorbed into the body but are degraded to uric acid by the gut. S-adenosylmethionine supplementation (beginning at 20 mg/kg/day orally) has been effective in greatly reducing the acute hospitalization episodes of 2 brothers with Arts syndrome, over a period of 10 yr. Treatment of PRPS superactivity is aimed at controlling the hyperuricemia with allopurinol, which inhibits xanthine oxidase, the last enzyme of the purine catabolic pathway. Uric acid production is reduced and is replaced by hypoxanthine, which is more soluble, and xanthine. The initial dose of allopurinol is 10-20 mg/kg/24 hr in children and is adjusted to maintain normal uric acid levels in plasma. The risk of xanthine stone formation is similar to that described for LND. A low purine diet (one free of organ meats, dried beans, and sardines), high fluid intake, and alkalization of the urine to establish a urinary pH of 6.0-6.5 is necessary. These measures control the hyperuricemia and urate nephropathy but do not affect the neurologic symptoms. There is no known treatment for the neurologic complications.

**Adenylosuccinate Lyase Deficiency (Succinylpurinuria)**
Adenylosuccinase lyase deficiency is an inherited deficiency of de novo purine synthesis in humans. adenylosuccinase lyase is an enzyme that catalyzes 2 pathways in de novo synthesis and purine nucleotide recycling. These are the conversion of succinylaminomimidazole carboxamide ribotide to aminoimidazole carboxamide ribotide (AICAR) in the de novo synthesis of purine nucleotides and the conversion of adenylosuccinate (S-AMP) into AMP; the second step in the conversion of inosine monophosphate (IMP) into AMP, in the purine nucleotide cycle. Adenylosuccinase lyase deficiency results in the accumulation in urine, cerebrospinal fluid, and, to a smaller extent, in plasma, of succinylaminomidazole carboxamide riboside and succinyladenosine (S-Ado), the dephosphorylated derivatives of succinylaminomidazole carboxamide ribotide and S-AMP, respectively.

**Genetics**
This is an autosomal recessive disorder; the gene has been mapped to chromosome 22q13.1-q13.2 and approximately 20 gene mutations have been identified. Laboratory investigations show grossly raised succinylpurines in urine and cerebrospinal fluid, which are normally undetectable.

**Clinical Manifestations**
Clinical manifestations include varying degrees of psychomotor retardation, generally accompanied by a seizure disorder and/or autistic-like behaviors (poor eye contact and repetitive behaviors). Neonatal seizures and a severe infantile epileptic encephalopathy are often the first manifestations of this disorder. Others demonstrate moderate to severe intellectual disability sometimes associated with growth retardation and muscle hypotonia. One reported case, a girl, tested in the mild range of intellectual disability. The form with profound intellectual disability has been designated type I; the variant case with mild intellectual disability as type II. Other patients have an intermediate clinical symptom pattern with moderately delayed psychomotor development, seizures, stereotypies, and agitation.

**Pathology**
CT and MRI of the brain may show hypotrophy or hypoplasia of the cerebellum, particularly the vermis. It is proposed that rather than being caused by purine nucleotide depletion, the symptoms are from the neurotoxic effects of accumulating succinylpurines. The ratio of S-Ado: succinylaminomimidazole carboxamide riboside has been linked to phenotype severity, suggesting that succinylaminomimidazole carboxamide riboside is the more toxic compound and that S-Ado might be neuroprotective.

The laboratory diagnosis is based on the presence in urine and cerebrospinal fluid of succinylaminomimidazole carboxamide riboside and S-Ado, both normally undetectable.

**Treatment**
No successful treatment has been demonstrated for this disorder. S-adenosylmethionine supplementation therapy was tested for 6 mo for a baby diagnosed in the early postnatal period, but no amelioration of symptoms were noted, providing further evidence that the disorder arises from nucleotide toxicity rather than depletion. Prenatal diagnosis has been reported. Systematic screening is suggested in infants and children with unexplained psychomotor retardation, and/or seizures disorder.

**Aminoimidazole Carboxamide Ribotide Transformylase/Inosine Monophosphate Cyclohydrolase Deficiency**
AICAR riboside is the dephosphorylated product of AICAR, also termed ZMP. Along with its di- and triphosphates, ZMP accumulates in red blood cells and fibrocytes in inherited deficiency of the bifunctional enzyme AICAR transformylase/IMP cyclohydrolase (ATIC), which catalyzes the conversion of AICAR to formyl-ATIC.

**Genetics**
This is an inborn error of purine biosynthesis caused by a mutation of the ATIC gene effecting AICAR transformylase activity. In a single
reported case AICAR transformylase was profoundly deficient, whereas the IMP cyclohydrolase level was 40% of normal.

Clinical Features
The disorder is described in a female infant with profound intellectual disability, epilepsy, dysmorphic features (prominent forehead and metopic suture, brachycephaly, wide mouth with thin upper lip, low-set ears, and prominent clitoris because of fused labia minora), and congenital blindness.

Laboratory
Urinary screening with the Bratton-Marshall test to detect AICA resulted in the identification of this disorder. The transformylase was found to be deficient in fibroblasts in this disorder, confirming diagnosis.

Treatment
No successful treatment is described.

DISORDERS RESULTING FROM ABNORMALITIES IN PURINE CATABOLISM

Myoadenylate Deaminase Deficiency
(Muscle Adenosine Monophosphate Deaminase Deficiency)
Myoadenylate deaminase is a muscle-specific isoenzyme of AMP deaminase that is active in skeletal muscle. During exercise, the deamination of AMP leads to increased levels of IMP and ammonia in proportion to the work performed by the muscle. Two forms of myoadenylate deaminase deficiency are known: an inherited (primary) form that may be asymptomatic or associated with cramps or myalgia with exercise, and a secondary form that may be associated with other neuromuscular or rheumatologic disorders.

Clinical Manifestations
Clinical manifestations are most commonly isolated muscle weakness, fatigue, myalgias following moderate-to-vigorous exercise, or cramps. Myalgia may be associated with an increased serum creatine kinase level and detectable electromyelographic abnormalities. Muscle wasting or histologic changes on biopsy are absent. The age of onset may be as early as 8 mo of life with approximately 25% of cases recognized between 2 and 12 yr of age. The enzyme defect has been identified in asymptomatic family members. Secondary forms of muscle AMP deaminase deficiency have been identified in Werner-Hoffmann disease, Kugelberg-Welander syndrome, polyneuropathies, and amyothrophic lateral sclerosis (see Chapter 612.2). The metabolic disorder involves the purine nucleotide cycle. As shown in Figure 89-2, the enzymes involved in this cycle are AMP deaminase, S-AMP synthetase, and S-AMP lyase. It is proposed that muscle dysfunction in AMP deaminase deficiency results from impaired energy production during muscle contraction. It is unclear how individuals may carry the deficit and be asymptomatic. In addition to muscle dysfunction, a mutation of liver AMP deaminase has been proposed as a cause of primary gout, leading to overproduction of uric acid.

Genetics
The inherited form of the disorder is an autosomal recessive trait. AMP-D1, the gene responsible for encoding muscle AMP deaminase, is located on the short arm of chromosome 1 (1p13-21). Population studies reveal that a mutant allele is found at high frequency in white populations, but alternative splicing of the gene can result in removal of the mutation and normal enzyme function. As a result, the disorder is usually screened by performing the forearm ischemic exercise test. The elevation of venous plasma ammonia following exercise that is seen in normal subjects is absent in AMP deaminase deficiency.

Laboratory
The final diagnosis is made by histochemical or biochemical assays of a muscle biopsy. The primary form is distinguished by the finding of enzyme levels below 2% with little or no immunoprecipitable enzyme.

Affected individuals are advised to exercise with caution to prevent rhabdomyolysis and myoglobinuria.

Treatment
Although there are no documented fully effective treatments, it has been proposed that enhancing the rate of replenishment of the ATP pool might be beneficial. Using this rationale treatment with ribose (2-60 g/24 hr orally, in divided doses) or xylitol, that is converted to ribose, has been reported to improve endurance and muscle strength in some cases but is ineffective in others. Genetic approaches may be feasible in the future for inherited cases while treatment of the underlying condition is essential in secondary cases.

Adenosine Deaminase Deficiency
See Chapter 126.1.

Purine Nucleoside Phosphorylase Deficiency
See Chapter 126.2.

Xanthine Oxidoreductase Deficiency (Hereditary Xanthinuria/Molybdenum Cofactor Deficiency)
Xanthine oxidoreductase (XOR) is the catalytic enzyme in the final step of the purine catabolic pathway and oxidizes hypoxanthine to xanthine and xanthine to uric acid. Because XOR exists in 2 forms, xanthine dehydrogenase and xanthine oxidase, the deficiency is also referred to as xanthine dehydrogenase/xanthine oxidase deficiency. Xanthine, the immediate precursor of uric acid, is less soluble than uric acid in urine and deficiency of the enzyme results in xanthinuria. XOR deficiency may occur in isolated form (xanthinuria type 1), in a combined form involving XOR and aldehyde oxidase deficiencies (xanthinuria type II), or multiple deficiencies of XOR, aldehyde oxidase, and sulfite oxidase (molybdenum cofactor deficiency). All 3 forms result in an almost total replacement of uric acid by hypoxanthine and xanthine in urine, while plasma uric acid is very low or undetectable.

Patients with the isolated form can be asymptomatic or have mild symptoms; renal stones, often not visible on radiography, are a risk for renal damage and may appear at any age, when patients may present with loin pain or renal insufficiency. For type II xanthinuria the clinical presentation is similar to type I, but patients also have aldehyde oxidase deficiency, which has no known clinical attributes. Molybdenum cofactor deficiency arises from inherited deficiency of molybdenum cofactor synthase, which affects all 3 molybdoenzymes, and like isolated sulfite oxidase deficiency, it usually presents with neonatal feeding problems, neonatal seizures, increased or decreased muscle tone, ocular lens dislocation, severe intellectual disability, and death in early childhood. Milder cases have presented with lens dislocation only.

Genetics
The inheritance of all 3 types of xanthinuria is complex and autosomal recessive. Type I results from mutations in the human XDH gene located on chromosome 2p22. Type II xanthinuria arises from mutations in the molybdenum cofactor synthase gene located on chromosome 18q12.2; this encodes molybdenum cofactor sulfurate, which is essential for the activity of both XOR and aldehyde oxidase. Type III xanthinuria (XOR, aldehyde oxidase and sulfite oxidase deficiencies) can arise from functional mutations in any of 3 genes: MOCS1 (encoding 2 enzymes for synthesis of the precursor via a bicistronic transcript), MOCS2 (encoding molybdopterin synthase), or GPHN (encoding gephyrin), located at 6p21.2, 5q11.2, and 14q23.3, respectively.

Laboratory
Diagnosis is made initially by measuring plasma and/or urinary concentrations of uric acid. Plasma uric acid is very low or absent (<1 mg/dL). Urinary uric acid is reduced, being replaced by xanthine and hypoxanthine. Type II patients can be distinguished by the absence in urine of methyl-2-pyridone-carboxamide, the product of nicotinamide (niacin) breakdown by aldehyde oxidase. Alternately, type II patients
can be distinguished from type I by their inability to oxidize a test dose of allopurinol to oxypurinol, via aldehyde oxidase. Molybdenum cofactor deficiency is distinguished by an additional excessive urinary excretion of sulfite and other sulfur-containing metabolites such as sulfocysteine.

Enzyme assay of XOR is not usually offered because it requires jejunal or liver biopsy, as these are the only human tissues that contain appreciable amounts of the enzyme. Sulfite oxidase and the molybdenum cofactor synthase can be measured in liver and fibroblasts. Molecular genetic analysis can be used to confirm diagnosis by searching for functional mutations among the three groups of genes.

**Treatment**
Although isolated deficiency is generally benign, treatment with a diet of low purines and low fructose (which reduces ATP breakdown to xanthine) with increased fluid intake is recommended. Allopurinol is not recommended. The prognosis for molybdenum cofactor deficiency has previously been very poor, but trials of cyclic pyranopterin monophosphate are promising.

**DISORDERS OF PYRIMIDINE METABOLISM**

The pyrimidines are the building blocks of DNA and RNA and involved in the formation of active intermediates in carbohydrate and phospholipid metabolism (e.g., uridine diphosphate glucose, cytidine diphosphate choline), glucuronidation in detoxification processes (uridine diphosphate), and glycosylation of proteins and lipids.

The essential precursor for pyrimidine biosynthesis is carbamyl-phosphate, which is shared with the urea cycle. Consequently, proximal blockages of the urea cycle results in carbamyl-phosphate overflowing into the pyrimidine pathway. Pyrimidine synthesis differs from that of purines in that the single pyrimidine ring is first assembled to form orotic acid and then linked to ribose phosphate to form the central pyrimidine nucleotide uridine monophosphate (UMP). The pyrimidines bases, uracil and thymine, are catabolized in 4 steps, as shown in Figure 89-3. Eight disorders of pyrimidine metabolism are reviewed. Purine catabolism has an easily measurable end point in uric acid; however, there is no equivalent compound in pyrimidine catabolism. The first defect (hereditary orotic aciduria) is in the de novo synthetic pathway, 1 defect (thymidine kinase) is part of pyrimidine salvage, and the other disorders involve overactivity (in 1 syndrome) or defects in the pyrimidine degradation pathway. Pyrimidine disorders may present as anemia, neuropathologies, or multisystem mitochondrial disorders. The first 3 steps of the degradation pathways for thymine and uracil, respectively, make use of the same enzymes (DPD, DPH, and UP). These 3 steps result in the conversion of uracil into β-alanine. There is increasing evidence that pyrimidines play an important role in the regulation of the nervous system. Reduced production of the neurotransmitter function of γ-aminobutyric acid and β-alanine is hypothesized to produce clinical symptoms. Clinically, pyrimidine disorders may be overlooked because they are rare and their symptoms are not highly specific; however, they should be considered as possible causes of anemia and neurologic disease and are a contraindication for treatment of cancer patients with certain pyrimidine analogs.

**Uridine Monophosphate Synthase Type 1 Deficiency (Hereditary Orotic Aciduria)**
Hereditary orotic aciduria is a disorder of pyrimidine synthesis associated with deficient activity of the last 2 steps of the de novo pyrimidine synthetic pathway, orotate phosphoribosyltransferase, orotidine-5′-monophosphate decarboxylase (ODC). The activities of these 2 steps reside in separate domains of a bifunctional protein, UMP synthase. This catalyzes the 2-step conversion of orotic acid to UMP, via orotidine monophosphate. Hereditary orotic aciduria (UMP synthase deficiency) results in the excessive accumulation of orotic acid.

**Genetics**
UMP synthase deficiency is inherited as an autosomal recessive disorder, with both functional domains encoded on a single gene, UMPS, which is located on the long arm of chromosome 3 (3q13). Theoretically, random mutations in the gene should have equal chances of producing either orotate phosphoribosyltransferase or ODC deficiency, but there has been only a single case of ODC deficiency reported. Genetic metabolic defects that involve 4 of the 6 enzymes associated with the urea cycle may also result in orotic aciduria, secondary to PPRP depletion resulting from a substantial increased flux through the pyrimidine synthesis pathway.

**Clinical**
Clinically patients with hereditary orotic aciduria (UMPS type 1 deficiency) have a macrocytic hypochromic megaloblastic anemia that is unresponsive to the usual forms of therapy (iron, folic acid, and vitamin B12), and may develop leukopenia. Onset is usually in first months of life. Untreated, this disorder can lead to developmental disability, intellectual disability, failure to thrive, cardiac disease, strabismus, crystalluria, and occasional ureteric obstruction. Renal function is generally normal. Heterozygotes may have mild orotic aciduria but are not otherwise affected. The clinical features are thought to be related to pyrimidine nucleotide depletion. Metabolites derived from several pharmacologic agents (5-azauridine, allopurinol) can produce secondary orotic aciduria and orotidinuria by specifically inhibiting the ODC step of UMP synthase. Orotic aciduria may also occur in association with parenteral nutrition, essential amino acid deficiency, and Reye syndrome.

**Laboratory**
The enzymatic defect may be demonstrated in liver, lymphoblasts, erythrocytes, leukocytes, and cultured skin fibroblasts. A carrier detection test is available, as is prenatal diagnosis, although the condition is treatable.

**Dihydropyrimidine Dehydrogenase Deficiency (Thymine-Uraciluria, Pyrimidinuria)**
DPD catalyzes the initial and rate-limiting step in the degradation of the pyrimidine bases uracil and thymine. DPD has been identified in most tissues, with the highest activity being in lymphocytes.

**Genetics**
DPD deficiency is an autosomal recessive disorder, with the DYPD gene mapping to chromosome 1p22, with at least 32 polymorphisms detected. It is estimated that the frequency of heterozygosity may be as high as 3%.

The clinical manifestations in children may include seizure disorder, intellectual disability and motor delay. Less frequent are growth retardation, microcephaly, autistic-like behavior, and ocular anomalies. Others do not show developmental abnormalities but may have milder neurological symptoms and language disorder. Unaffected cases have been reported, raising discussion about possible secondary gene effects. In most cases, there is an initial period of normal psychomotor development, followed by subsequent developmental delays. Symptoms may be linked to altered uracil, thymine, or β-alanine homeostasis. Because β-alanine is a structural analog of γ-aminobutyric acid and glycine, it has been proposed that it may affect inhibitory neurotransmission. DPD is the initial and rate-limiting enzyme in the inactivation of the neoplastic drug 5-fluorouracil, being responsible for 80% of its catabolism. Patients with partial DPD deficiency are at risk for developing a severe 5-fluorouracil-associated toxicity. In adult patients, neurotoxicity (headache, somnolence, visual illusions and memory impairment) linked to pyrimidinemia following 5-fluorouracil treatment for cancer is reported in previously healthy individuals.
Laboratory
DPD deficiency is characterized by a variable phenotype and diagnosed by the gross accumulation of thymine and uracil in urine (thymine-uraciluria), plasma and cerebrospinal fluid. Uric acid levels have been reported to be normal. Prenatal diagnosis has been reported.

Treatment
There is no established treatment for this disorder, however, patients with seizures do respond to anticonvulsant medications. DPYD*5 (rs1801159) and 1896 T>C (rs17376848) are potentially useful predictive markers of patients' responses to 5-FU chemotherapy.

Dihydropyrimidinase Deficiency (Dihydropyrimidinuria)
Dihydropyrimidinase (DPH) is the second enzyme in the 3-step degradation pathway of uracil and thymine. DPH deficiency is characterized by increased urinary excretion of dihydrouracil and dihydrothymine (dihydropyrimidinuria), as well as uracil and thymine. Similar to DPD deficiency, there is a variable clinical phenotype.

Genetics
This is an autosomal recessive disorder, with the DPYS gene mapped to chromosome 8q22. In 1 study there was no significant difference in residual activity between mutations observed in symptomatic and asymptomatic individuals, again similar to DPD deficiency. Population prevalence in a Japanese sample was 0.1%.

Clinical
Clinical manifestations are similar to DPD deficiency, which is evidence that defects in these sequential steps produce a common disorder. Symptoms in 3 unrelated affected cases include seizures with dysmorphic features and developmental delay in 2 of these cases. However, 3 unrelated infant and 2 adult asymptomatic cases were identified in a screening program for pyrimidine degradation disorders in Japan and were asymptomatic despite the accumulation of pyrimidine degradation products in body fluids.

Laboratory
Organic acid screening may identify increased amounts of uracil and thymine in urine. Oral loading tests with uracil, dihydrouracil, thymine, and dihydrothymine have been used to detect carriers of the deficiency. In symptomatic cases, treatment with β-alanine has been attempted with equivocal results. A single case of increased sensitivity to 5-fluorouracil has been reported.

Deficiency of β-Ureidopropionase (N-Carbamyl-β-Amino Aciduria)
The pyrimidine bases uracil and thymine are degraded via the consecutive action of 3 enzymes to β-alanine and β-aminoisobutyric acid, respectively. The third enzyme in the pathway is ureidopropionase, and its deficiency leads to N-carbamyl-β-amino aciduria. 3-ureidopropionase (3-UPA) acts as endogenous neurotoxin via inhibition of mitochondrial energy metabolism resulting in the initiation of secondary, energy-dependent excitotoxic mechanisms.

Genetics
Fluorescence in situ hybridization localized the human β-ureidopropionase gene, UPB1, to 22q11.2.

Clinical
Clinical manifestations in a reported case include muscular hypotonia, dystonic movements, and severe developmental delay.

Laboratory
Neuropathology involves both gray and white matter. Ureidopropionase deficiency leads to pathologic accumulation of 3-UPA in body fluids. Urinary analysis in a reported case showed elevated levels of N-carbamyl-β-alanine and N-carbamyl-β-aminoisobutyric acid (ureidoisobutyric acid). The enzyme is expressed only in the liver and no activity of β-ureidopropionase is detected in a liver biopsy.

Treatment
There is no known treatment for ureidopropionase deficiency.

Pyrimidine 5′-Nucleotidase Deficiency
Erythrocyte maturation is accompanied by RNA degradation and the release of mononucleotides. Pyrimidine 5′-nucleotidase is the first degradation enzyme of the pyrimidine salvage cycle and catalyzes the hydrolysis of pyrimidine 5′-nucleotides to the corresponding nucleosides. Enzyme deficiency results in the accumulation of high levels of cytidine and uridine nucleotides in the erythrocytes that, in turn, results in hemolysis. Deficiency of pyrimidine 5′-nucleotidase may be at least in part compensated in vivo by other nucleotidases or perhaps other nucleotide metabolic pathways.

Genetics
This is an autosomal recessive disorder involving the gene pyrimidine 5′-nucleotidase deficiency on chromosome 7 (7p13). Affected pyrimidine 5′-nucleotidase deficiency patients clinically present with a defect restricted to erythrocytes that is characterized by nonspherocytic hemolytic anemia with basophilic stippling. Other characteristic features include splenomegaly, increased indirect bilirubin, and hemoglobinuria. Lead is a powerful inhibitor of pyrimidine 5′-nucleotidase and assessment of lead levels should be included whenever hemolytic anemia, pyrimidine 5′-nucleotidase deficiency, and basophilic stippling are found together.

Laboratory
Diagnosis requires assay of erythrocyte UMP hydrolysis to form uridine and inorganic phosphate. The enzyme defect should be suspected in patients with nonspherocytic hemolytic anemia with basophilic stippling. The anemia is usually moderate, and transfusions are rarely necessary.

Treatment
There is no specific treatment. Splenectomy has not proved to be an effective treatment. Lead-induced acquired pyrimidine 5′-nucleotidase deficiency is treatable, unlike the congenital deficiency.

OVERACTIVE CYTOSOLIC 5′-NUCLEOTIDASE (PYRIMIDINE NUCLEOTIDE DEPLETION)
Pyrimidine nucleotide depletion and overactive cytosolic 5′-nucleotidase, may lead to a neurodevelopmental disorder. Four unrelated patients showed 6-10-fold elevation in the activity of pyrimidine 5′-nucleotidase in fibroblasts with both purine and pyrimidine substrates. Investigation in cultured fibroblasts derived from these patients showed normal incorporation of purine bases into nucleotides but decreased incorporation of uridine and orotic acid.

Clinical
Clinical manifestations include developmental delay, seizures, ataxia, recurrent infections, severe language deficit, hyperactivity, short attention span, and aggressive behavior appearing within the first few years of life. Affected patients show electroencephalogram abnormalities. Metabolic testing is normal except for persistent hypouricosuria. It is proposed that increased catabolic activity and decreased pyrimidine salvage cause a deficiency of pyrimidine nucleotides.

Treatment
Treatment is with oral uridine based on compensating for the increased nucleotide catabolism. All reported patients treated with uridine showed improved speech and behavior, decreased seizure activity with discontinuation of seizure medications, and decreased frequency of infections.

Thymidine Phosphorylase Deficiency (Mitochondrial Neurogastrointestinal Encephalomyopathy)
Thymidine phosphorylase catalyzes the catabolism in mitochondria of thymidine to thymine. This enzyme is also known as "platelet-derived..."
endothelial cell growth factor” because of its angiogenic properties, or “gliostatin” indicating its inhibitory effects on glial cell proliferation. It has been implicated in mitochondrial nucleoside metabolism. Plasma thymidine level is increased more than 20-fold in patients compared to controls. Loss of function of thymidine phosphorylase causes mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), which is inherited as a single autosomal recessive disorder, causing mitochondrial DNA depletion and instability. In MNGIE, loss of thymidine phosphorylase activity causes toxic accumulations of the nucleosides thymidine and deoxyuridine that are incorporated by the mitochondrial pyrimidine salvage pathway and cause deoxynucleoside triphosphate pool imbalances.

Genetics
The TYMP gene encoding thymidine phosphorylase has been identified as the MNGIE gene and is mapped to chromosome 22q13.32-qter, but the protein is imported into mitochondria.

Clinical Manifestations
Clinical manifestations of MNGIE include ptosis, progressive external ophthalmoparesis, gastrointestinal dysmotility and malabsorption, cachexia, peripheral neuropathy, skeletal muscle myopathy and leukoencephalopathy.

Laboratory
Muscle biopsies typically reveal mitochondrial abnormalities. Screening is performed by detection of grossly raised thymidine and deoxyuridine in urine, which are normally absent. Confirmation of the diagnosis can be made by assay of thymidine phosphorylase activity in peripheral leukocytes. Molecular genetic analysis will show functional mutations in the TYMP gene. Increased thymidine and/or deoxyuridine nucleotides may cause mitochondrial nucleotide pool imbalance resulting in mitochondrial DNA alterations, in particular DNA depletion.

Treatment
Supportive treatment is indicated. There is no established therapy for MNGIE; bone marrow transplantation has been performed on several patients but no improvement in symptoms or progression of the disease has been reported. Allogeneic hematopoietic stem cell transplantation to restore thymidine phosphorylase activity and eliminate toxic metabolites is a potential therapy for MNGIE.

THYMIDINE KINASE 2 DEFICIENCY
Thymidine kinase 2 (TK2) is a key enzyme for the pyrimidine salvage pathway to provide precursor nucleotide for mitochondrial DNA. TK2 deficiency causes tissue-specific depletion of mitochondrial DNA. TK2 normally phosphorylates thymidine and deoxycytidine.

Genetics
The TK2 gene is located on chromosome 16q 22; the deficiency is inherited in an autosomal recessive manner.

Clinical
Clinically, affected individuals with TK2 deficiency have severe myopathy and depletion of muscular mitochondrial DNA in infancy.

Treatment
No specific treatment is available. Supportive treatment is indicated.

ACKNOWLEDGMENTS
Thanks to John A. Duley, PhD, of the University of Queensland, Brisbane, Australia, who reviewed the figures and made suggestions for the text; and to Lynette Fairbanks, PhD, of St. Thomas’ Hospital, London, who reviewed the text and figures.

Bibliography is available at Expert Consult.
**Bibliography**


**Disorders Linked to Purine Nucleotide Synthesis**


**Adenylsuccinate Lyase Deficiency (Succinylpurinuria)**


**Aicar Transformylase/Imp Cyclohydrolyase (ATIC) Deficiency (Aica-Ribosiduria)**


**Disorders Resulting from Abnormalities in Purine Catabolism**


**Xanthine Oxidoreductase Deficiency (Hereditary Xanthinuria/ Molybdenum Cofactor Deficiency)**


Disorders of Pyrimidine Metabolism


Dihydropyrimidinase Deficiency (Thymine-Uraciluria, Pyrimidinuria)


Dihydropyrimidinase Deficiency (Dihydropyrimidinuria)


Deficiency of Beta-Ureidopropionase (N-Carbamyl-Beta-Amino Aciduria)


Pyrimidine 5′-Nucleotidase Deficiency


Overactive Cytosolic 5′ Nucleotidase (Pyrimidine Nucleotide Depletion)


Ipata PL, Tozzi MG: Recent advances in structure and function of cytosolic IMP-GMP specific 5′-nucleotidase II (cN-II), Purinergic Signal 2:669–675, 2006.

Thymidine Phosphorylase Deficiency (Mitochondrial Neurogastrointestinal Encephalomyopathy-MNGIE)


Thymidine Kinase 2 (TK2) Deficiency


Hutchinson-Gilford progeria syndrome (progeria) is a rare, fatal, autosomal dominant segmental premature aging disease. With an estimated incidence of 1 in 4,000,000 live births and prevalence of 1 in 18 million, there were a total of 350 children living with progeria in 2013 worldwide. There is no gender, ethnic, or regional bias. Progeria is caused by a single base mutation in \( LMNA \), which results in the production of a mutant lamin A protein called progerin. Progerin is found in increased concentration in skin and the vascular wall of normal older compared to younger individuals, suggesting a role in normal aging. Children develop progressive atherosclerosis and die of heart attacks or strokes at a median age of 14.5 yr, most often between ages 5 and 20 yr.

**CLINICAL MANIFESTATIONS**

Children develop the appearance of accelerated aging. Physical appearance changes dramatically each year that the children age (Fig. 90-1).

**Dermatologic Changes**

Skin findings are often apparent as initial signs of progeria. These are variable in severity and include areas of discoloration, stippled pigmentation, tightened areas that can restrict movement, and areas of the trunk or legs where small (1-2 cm) soft, bulging skin is present. Although usually born with normal hair present, patients lose cranial hair within the first few years, and are left with soft, downy, sparse immature hair on the scalp, no eyebrows, and scant eye lashes.

**Failure to Thrive**

Children with progeria experience apparently normal fetal and early postnatal development. Within the first year of life, abnormalities in growth and body composition are readily apparent; severe failure to thrive ensues, heralding generalized lipodystrophy, with apparent wasting of limbs, circumoral cyanosis, and prominent veins around the scalp, neck, and trunk. The mean weight, which is normal at birth, decreases to below the third percentile for normal children despite adequate caloric intake for normal growth and normal resting energy expenditure. A retrospective data set of 35 children showed an average weight gain of only 0.44 kg/year, beginning at 24 mo of age and persisting throughout life. There is interpatient variation in weight gain, but the projected weight gain over time in an individual patient is constant, linear, and very predictable. Children with progeria reach a final height of approximately 1 m and weight of approximately 14 kg. Head circumference is normal. Weight deficit is more pronounced than height deficit and this, associated with the loss of subcutaneous fat, results in the emaciated appearance characteristic of children with progeria. Clinical problems caused by the lack of subcutaneous fat include insulin resistance, sensitivity to cold temperatures, and foot discomfort because of a lack of fat cushioning. Although overt diabetes is very unusual in progeria, approximately 30-40% of children suffer from insulin resistance.

**Ocular Abnormalities**

Tightened skin and a paucity of subcutaneous fat around the eyes causes most patients to sleep with eyelids partially open, resulting in corneal dryness and eye tearing. Patients can develop exposure keratopathy and/or corneal ulcers, which can disrupt sight. Artificial tears
Some degree of photophobia is common. During the day and taping or covering the eyes at night are recommended. Some degree of photophobia is common.

**Dental Abnormalities**

Dentition is severely delayed in development and crowded due to micrognathia. Eruption may be delayed for many months, and primary teeth may persist for the duration of life. Secondary teeth are present, but may or may not erupt. They sometimes erupt on the lingual and palatal surfaces of the mandibular and maxillary alveolar ridges, rather than in place of the primary incisors. In some but not all cases, extracting primary teeth promotes movement of secondary teeth into place.

**Bone and Cartilaginous Abnormalities**

Aberrent development of bone structure and bone density represents a unique skeletal dysplasia which is not based in malnutrition. Acroosteolysis of the distal phalanges, distal clavicular resorption and thin, tapered ribs are early signs of progeria that appear as early as 3 mo of age. Facial disproportion, a narrowed nasal bridge and retrognathia make intubation extremely difficult, and fiberoptic intubation is recommended. A pyriform chest structure and a small clavicle can lead to reducible shoulder dislocations (Fig. 90-1E). Long bone remodeling of the femoral head–neck axis following knee and ankle contractures results in coxa valga, straightening of the femoral head–neck axis to 125 degrees. The bony pelvis is normal and these changes give rise to a “horse riding” stance. Hip dysplasia is often progressive and may result in avascular necrosis, hip dislocation, and inability to bear weight. A pyriform chest structure and a small clavicle can lead to reducible shoulder dislocations (Fig. 90-1E).

**Cerebrovascular Arteriopathy and Stroke**

Cerebral infarction may occur while the child exhibits a normal electrocardiogram. The earliest incidence of stroke occurred at the age of 0.4 yr. More often they occur in the later yr. Radioangiographic evidence on MRI of infarction can be found in 60% of the patients, in whom half are clinically silent. Both large- and small-vessel disease is found; collateral vessel formation is extensive. Carotid artery occlusions are well documented, but infarction can occur in their absence. Propensity toward strokes and an underlying stiff vasculature make maintaining adequate blood pressure through hydration (i.e., habitually drinking well) a priority in progeria; special care should be taken when considering maintenance of consistent blood pressure during general anesthesia, airplane trips, and hot weather.

**Normally Functioning Systems**

Liver, kidney, thyroid, immune, gastrointestinal, and neurologic systems (other than stroke-related) remain intact. Intellect is normal for age.

**Laboratory Findings**

The most consistent laboratory findings are low serum leptin and insulin resistance. Platelet count is often moderately high. Lipid panels, blood chemistries, endocrine and coagulation and other tests are generally normal.

**MOLECULAR PATHOGENESIS**

Mutations in the *LMNA* gene cause progeria. The normal *LMNA/C* gene encodes the proteins lamins A and C, of which only lamin A is associated with human diseases. The lamin proteins are the principal proteins of the nuclear lamina, a complex molecular interface located between the inner membrane of the nuclear envelope and chromatin. The integrity of the lamina is central to many cellular functions, creating and maintaining structural integrity of the nuclear scaffold, DNA replication, RNA transcription, organization of the nucleus, nuclear pore assembly, chromatin function, cell cycling, and apoptosis.

Progeria is almost always a sporadic autosomal dominant disease. There is 1 proven case of mosaicism. Progeria is caused by the accelerated use of an alternative, internal splice site that results in the deletion of 150 base pairs in the 3′ portion of exon 11 of the *LMNA* gene. In approximately 90% of cases, this results from a single C to T transition at nucleotide 1824 that is silent (Gly608Gly), but optimizes an internal splice site within exon 11. The remaining 10% of cases possess 1 of several single base mutations within the intron 11 splice donor site,
thus reducing specificity for this site and altering the splicing balance in favor of the internal splice. Subsequent to all of these mutations, translation followed by posttranslational processing of the altered messenger RNA produces progerin, a shortened abnormal lamin A protein with a 50-amino-acid deletion near its C-terminal end. An understanding of the posttranslational processing pathway and how it is altered to create progerin has led to a number of treatment prospects for the disease.

Both lamin A and progerin possess a farnesyl side group attached during posttranslational processing. This is a lipophilic moiety which facilitates intercalation of proteins into the inner nuclear membrane where most of the lamin and progerin functions are performed. For normal lamin A, loss of the farnesyl anchor releases prelamin from the nuclear membrane, rendering it soluble for autophagic degradation. However, progerin retains its farnesyl moiety. It remains anchored to the membrane, binding other proteins, causing blebbing of the nucleus, disrupting mitosis, and altering gene expression.

Disease in progeria is produced by a dominant negative mechanism; it is the action of progerin, not the diminution of lamin A that causes the disease phenotype. The severity of disease is determined in part by progerin levels, which are regulated by the particular mutation, tissue type, or other factors influencing use of the internal splice site.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**

Overall, the constellation of small body habitus, bone, hair, subcutaneous fat, and skin changes results in the marked physical resemblance among patients with progeria (Fig. 90-2). For this reason, clinical diagnosis can be achieved or excluded with relative confidence even at young ages, though there have been a few cases of low progerin-expressing patients with extremely mild signs. Clinical suspicion should be followed by LMNA genetic sequence testing. The disorders that resemble progeria are those grouped as the senile-like syndromes and include Wiedemann-Rautenstrauch syndrome, Werner syndrome, Cockayne syndrome, Rothmund-Thomson syndrome, restrictive dermopathy, and Nestor-Guillermo progeria syndrome (Table 90-1). Patients often fall under none of these diagnoses and represent ultrarare, unnamed progeroid laminopathies that carry either non–progerin-producing mutations in lamin or the lamin-associated enzyme Zmpste24, or progeroid syndromes without lamin mutations.

![Figure 90-2. Two unrelated children with progeria. Note the physical resemblance of each to the other.](Photo courtesy of The Progeria Research Foundation.)

<table>
<thead>
<tr>
<th>Table 90-1</th>
<th>Features of Hutchinson-Gilford Progeria Syndrome and Disorders That Resemble It</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HUTCHINSON-GILFORD PROGERIA SYNDROME</strong></td>
<td><strong>WIEDEMANN-RAUTENSTRAUCH SYNDROME</strong></td>
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<tr>
<td>Causative gene</td>
<td>LMNA</td>
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<tr>
<td>Inheritance</td>
<td>Dominant</td>
</tr>
<tr>
<td>Onset</td>
<td>Infancy</td>
</tr>
<tr>
<td>Hair loss</td>
<td>+Total</td>
</tr>
<tr>
<td>Skin thinning</td>
<td>+</td>
</tr>
<tr>
<td>Subcutaneous fat loss</td>
<td>+</td>
</tr>
<tr>
<td>Skin calcification</td>
<td>–</td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td>–</td>
</tr>
<tr>
<td>Cataracts</td>
<td>–</td>
</tr>
<tr>
<td>Short stature</td>
<td>+</td>
</tr>
<tr>
<td>Coxa valga</td>
<td>+</td>
</tr>
<tr>
<td>Acroosteolysis</td>
<td>+</td>
</tr>
<tr>
<td>Mandibular dysplasia</td>
<td>+</td>
</tr>
<tr>
<td>Vasculopathy</td>
<td>+</td>
</tr>
<tr>
<td>Voice abnormality</td>
<td>+</td>
</tr>
<tr>
<td>Diabetes</td>
<td>–</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>+</td>
</tr>
<tr>
<td>Dental abnormality</td>
<td>+</td>
</tr>
</tbody>
</table>

Children with progeria develop a severe premature form of atherosclerosis. Prior to death, cardiac decline with left-sided hypertrophy, valvular insufficiency, and pulmonary edema develop; neurovascular decline with transient ischemic attack, strokes, and occasionally seizures can result in significant morbidity. Death occurs as a result of heart attack (~80%) and stroke (~20%), generally between age 5 and 20 yr, with a median life span of 14.5 yr.

No specific FDA-approved treatment for this condition exists. Growth hormone has resulted in increased rate of weight gain and overall size when administered at 0.05 mg/kg/day SC, but weight still remained well below that seen in normal children. Low-dose aspirin therapy is recommended at 2 mg/kg body weight per day, as an extension of what is known about decreasing cardiovascular risk in the general at-risk adult population. It is not known whether growth hormone or low-dose aspirin has any effect on morbidity or mortality.

The first potentially beneficial treatment prospect for progeria was published in 2011. Inhibiting posttranslational progerin farnesylation with a drug named lonafarnib was aimed at preventing this disease-causing protein from anchoring to the nuclear membrane where it carries out much of its damage. A prospective single-arm clinical trial was initiated with a cohort of 25 progeria patients between 3 and 16 yr of age, treated for a minimum of 2 yr (NCT00425607). Lonafarnib was well tolerated; the most common side effects were diarrhea, nausea, and loss of appetite, which generally improved with time. Subgroups of patients experienced increased rate of weight gain, decreased vascular stiffness measured via improved carotid-femoral wave velocity, and carotid artery echodensity, increased radial bone structural rigidity, improved sensorineural hearing, and early evidence of decreased headache, transient ischemic attack and stroke rates. Dermatologic, dental, joint contracture, insulin resistance, lipodystrophy, bone mineral density, and joint contractures were unaffected by drug treatment. The evidence for improved cardiovascular status in children with progeria is most encouraging. A study published in 2014 demonstrated increased estimated lifespan for children with progeria taking farnesylation inhibitors such as lonafarnib.

An ongoing clinical trial which adds pravastatin and zoledronate, 2 FDA-approved drugs, to the lonafarnib regimen is similarly aimed at inhibiting progerin farnesylation (NCT00916747).

The Progeria Foundation (www.progeriaresearch.org) maintains an international registry, diagnostics program, and complete patient care manual and coordinates clinical treatment trials.

Bibliography is available at Expert Consult.
Bibliography


mechanisms for heme biosynthesis that are influenced by pubertal development. Homozygous forms of the hepatic porphyrias may manifest clinically prior to puberty. Children who are heterozygous for inherited hepatic porphyrias may present with nonspecific and unrelated symptoms, and parents often request advice about long-term prognosis and express concerns about drugs that may exacerbate these conditions.

The DNA sequences and chromosomal locations are established for the human genes of the enzymes in this pathway, and multiple disease-related mutations have been found for each porphyria. The inherited porphyrias display autosomal dominant, recessive or X-linked inheritance. Although initial diagnosis of porphyria by biochemical methods remains essential, it is especially important to confirm the diagnosis by demonstrating a specific gene mutation(s).

**THE HEME BIOSYNTHETIC PATHWAY**

Heme is required for a variety of hemoproteins such as hemoglobin, myoglobin, respiratory cytochromes, and cytochrome P450 enzymes (CYPs). It is believed that the 8 enzymes in the pathway for heme biosynthesis are active in all tissues. Hemoglobin synthesis in erythroid precursor cells accounts for approximately 85% of daily heme synthesis in humans. Hepatocytes account for most of the rest, primarily for synthesis of CYPs, which are especially abundant in the liver endoplasmic reticulum, and turn over more rapidly than many other hemoproteins, such as the mitochondrial respiratory cytochromes. Pathway intermediates are the porphyrin precursors δ-aminolevulinic acid (ALA, also known as 5-aminolevulinic acid) and porphobilinogen (PBG), and porphyrins (mostly in their reduced forms, known as porphyrinogens) (Fig. 91-1). At least in humans, these intermediates do not accumulate in significant amounts under normal conditions or have important physiologic functions.

A deficiency of each enzyme in the pathway is associated with a specific porphyria (Table 91-1). The first enzyme, ALA synthase (ALAS), occurs in 2 forms. An erythroid specific form, termed ALAS2, is deficient in X-linked sideroblastic anemia, as a result of mutations of the ALAS2 gene on chromosome Xp11.2. Gain of function mutations of ALAS2 because of deletions in the last exon cause X-linked protoporphyria (XLP), a cutaneous porphyria which is phenotypically identical to EPP.

Regulation of heme synthesis differs in the 2 major heme-forming tissues. Liver heme biosynthesis is primarily controlled by ALAS1. Synthesis of ALAS1 in liver is regulated by a “free” heme pool (see Fig. 91-1), which can be augmented by newly synthesized heme or by existing heme released from hemoproteins and destined for breakdown to biliverdin by heme oxygenase.

In the erythron, novel regulatory mechanisms allow for the production of the very large amounts of heme needed for hemoglobin synthesis. The response to stimuli for hemoglobin synthesis occurs during cell differentiation, leading to an increase in cell number. Also, unlike the liver, heme has a stimulatory role in hemoglobin formation, and the stimulation of heme synthesis in erythroid cells is accompanied by increases not only in ALAS2, but also by sequential induction of other heme biosynthetic enzymes. Separate erythroid-specific and nonerythroid or “housekeeping” transcripts are known for the first 4 enzymes in the pathway. The separate forms of ALAS are encoded by genes on different chromosomes, but for each of the other 3, erythroid and nonerythroid transcripts are transcribed by alternative promoters in the same gene. Heme also regulates the rate of its synthesis in erythroid cells by controlling the transport of iron into reticulocytes.

Intermediates of the heme biosynthetic pathway are efficiently converted to heme and, normally, only small amounts of the intermediates are excreted. Some may undergo chemical modifications before excretion. Whereas the porphyrin precursors ALA and PBG are colorless, nonfluorescent, and largely excreted unchanged in urine, PBG may degrade to colored products such as the brownish pigment called porphobilin or spontaneously polymerize to uroporphyrins. Porphyrins are red in color and display bright red fluorescence when exposed to long wavelength UV light. Porphyrinogens, which are colorless and nonfluorescent, are the reduced form of porphyrins, and when they

**Chapter 91  
The Porphyrias**

Manisha Balwani, Robert J. Desnick, and Karl E. Anderson

Porphyrias are metabolic diseases resulting from altered activities of specific enzymes of the heme biosynthetic pathway. These enzymes are most active in bone marrow and liver. Erythropoietic porphyrias, in which overproduction of heme pathway intermediates occurs primarily in bone marrow erythroid cells, usually present at birth or in early childhood with cutaneous photosensitivity, or in the case of congenital erythropoietic porphyria (CEP), even in utero as nonimmune hydrops. Erythropoietic protoporphyria (EPP) is the most common porphyria in children and of most interest to pediatricians. Most porphyrias are hepatic, with overproduction and initial accumulation of porphyrin precursors or porphyrins in the liver. Activation of hepatic porphyrias is very rare during childhood, reflecting the distinct hepatic regulatory
Figure 91-1 Enzymes and intermediates of the heme biosynthetic pathway. The pathway is regulated in the liver by the end product, heme, mainly by feedback repression (dashed arrow).
<table>
<thead>
<tr>
<th>Disease (Abbreviation)</th>
<th>Enzyme (Abbreviation)</th>
<th>Inheritance</th>
<th>Presentation</th>
<th>Hepatic</th>
<th>Erythropoietic</th>
<th>Acute/Neurologic</th>
<th>Cutaneous</th>
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<tr>
<td>X-Linked protoporphyria (XLP)</td>
<td>δ-Aminolevulinate synthase 2 (ALAS2)</td>
<td>X-linked</td>
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<td>δ-Aminolevulinic acid dehydratase (ALAD)</td>
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<td>Congenital erythropoietic porphyria (CEP)</td>
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<td>Protoporphyrinogen oxidase (PPOX)</td>
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<td>Homozygous dominant</td>
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<td>Erythropoietic protoporphyria (EPP)</td>
<td>Ferrochelatase (FECH)</td>
<td>Autosomal recessive (most commonly heteroallelic with hypomorphic allele)</td>
<td>Childhood</td>
<td></td>
<td></td>
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<td>X</td>
</tr>
</tbody>
</table>

*ADP and HEP are considered primarily hepatic porphyrias, but substantial increases in erythrocyte zinc protoporphyrin suggest an erythropoietic component.
†PCT is a result of inhibition of hepatic UROD. Autosomal dominant inheritance of a partial deficiency of UROD is a predisposing factor in cases defined as familial (type 2) PCT.
The 3 Most Common Human Porphyrias and Their Major Features

<table>
<thead>
<tr>
<th>Presenting Symptoms</th>
<th>Exacerbating Factors</th>
<th>Most Important Screening Tests</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Acute intermittent porphyria</td>
<td>Neurologic, adult onset</td>
<td>Drugs (mostly P450-inducers), progesterone, dietary restriction</td>
<td>Urinary porphobilinogen</td>
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<td>Porphyria cutanea tarda</td>
<td>Skin blistering and fragility (chronic), adult onset</td>
<td>Iron, alcohol, smoking, estrogens, hepatitis C, HIV, halogenated hydrocarbons</td>
<td>Plasma (or urine) porphyrins</td>
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<tr>
<td>Erythropoietic protoporphiria</td>
<td>Skin pain and swelling (mostly acute), childhood onset</td>
<td>Erythrocyte (or plasma) porphyrins</td>
<td>Beta-carotene</td>
</tr>
</tbody>
</table>

accumulate are readily autoxidized to the corresponding porphyrins when outside the cell. Only the type III isomers of uroporphyrinogen and coproporphyrinogen are converted to heme (see Fig. 91-1).

ALA and PBG are excreted in urine. Excretion of porphyrins and porphyrinogens in urine or bile is determined by the number of carboxyl groups. Those with many carboxyl groups, such as uroporphyrin (octacarboxyl porphyrin) and heptacarboxyl porphyrin, are water soluble and readily excreted in urine. Those with fewer carboxyl groups, such as protoporphyrin (dicarboxyl porphyrin), are not water soluble and are excreted in bile and feces. Coproporphyrin (tetracarboxyl porphyrin) is excreted partly in urine and partly in bile. Because coproporphyrin I is more readily excreted in bile than is coproporphyrin III, impaired hepatobiliary function may increase total urinary coproporphyrin excretion and the ratio of these isomers.

**Classification and Diagnosis of Porphyrias**

Two classification schemes reflect either the underlying pathophysiology or clinical features, and both are useful for diagnosis and treatment (see Table 91-1). In hepatic and erythropoietic porphyrias, the source of excess production of porphyrin precursors and porphyrins is the liver and bone marrow, respectively. Acute porphyrias cause neurologic symptoms that are associated with increases of 1 or both of the porphyrin precursors, ALA and PBG. In the cutaneous porphyrias, photosensitivity results from transport of porphyrins in blood from the liver or bone marrow to the skin. Dual porphyria refers to the very rare cases of porphyria with deficiencies of 2 different heme pathway enzymes.

It is notable that, porphyria cutanea tarda (PCT), acute intermittent porphyria (AIP), and EPP in that order the 3 most common porphyrias considering all age groups are very different in clinical presentation, precipitating factors, methods of diagnosis, and effective therapy (Table 91-2). Two of the 4 acute porphyrias, hereditary coproporphyria (HCP) and variegate porphyria (VP), can also cause lesions indistinguishable from PCT (see Table 91-1). CEP causes more severe blistering lesions, often with secondary infection and mutilation. EPP and XLP have the same phenotype and are distinct from the other cutaneous porphyrias in causing nonblistering photosensitivity that occurs acutely after sun exposure. EPP is also the most common porphyria to become manifest before puberty.

**First-Line Laboratory Diagnostic Testing**

A few sensitive and specific first-line laboratory tests should be obtained whenever symptoms or signs suggest the diagnosis of porphyria. If a first-line or screening test is significantly abnormal, more comprehensive testing should follow to establish the type of porphyria. Overuse of laboratory tests for screening can lead to unnecessary expense and even delay in diagnosis. In patients who present with a past diagnosis of porphyria, laboratory reports that were the basis for the original diagnosis must be reviewed, and if these were inadequate, further testing considered.

Acute porphyria should be suspected in patients with neurovisceral symptoms such as abdominal pain after puberty, when initial clinical evaluation does not suggest another cause, and urinary porphyrin precursors (ALA and PBG) and total porphyrins should be measured. Urinary PBG is virtually always increased during acute attacks of acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), and is not substantially increased in any other medical conditions. Therefore, this measurement is both sensitive and specific. A method for rapid, in-house testing for urinary PBG, such as the Trace PBG kit (Thermo Scientific, 1-800-640-0640), should be available in-house at all major medical facilities. Results from spot (single void) urine specimens are highly informative because very substantial increases are expected during acute attacks of porphyria. A 24 hr collection can unnecessarily delay diagnosis. The same spot urine specimen should be saved for quantitative determination of ALA and PBG to confirm the qualitative PBG result and total porphyrins. This will detect patients with ALA dehydratase porphyria (ADP) and some cases of HCP and VP, as urinary porphyrins may remain increased longer than porphyrin precursors in the latter disorders. Measurement of urinary porphyrins alone should be avoided for screening, because these are often increased in many disorders other than porphyrias, such as chronic liver disease, and misdiagnoses of porphyria can result from minimal increases in urinary porphyrins that have no diagnostic significance.

PBG is a colorless pyrrole that forms a violet pigment with Ehrlich reagent (p-dimethylaminobenzaldehyde). Other substances, principally urobilinogen, also react with Ehrlich aldehyde. A reliable quantitative method for both ALA and PBG, which uses small anion and cation exchange columns to separate interfering substances before adding Ehrlich reagent, has been available for many years. ALA is reacted to form a pyrrole, which is then also measured using Ehrlich reagent. The Trace PBG kit to detect increased PBG is based on this method.

**Blistering Cutaneous Porphyrias**

Blistering skin lesions caused by porphyria are virtually always accompanied by increases in total plasma porphyrins. A fluorometric method is preferred, because the porphyrins in plasma and VP are mostly covalently linked to plasma proteins and may be less readily detected by high-pressure liquid chromatography. The normal range for plasma porphyrins is somewhat increased in patients with end-stage renal disease. Urinary porphyrins are also increased in these porphyrias, but also in many other medical conditions.

**Nonblistering Cutaneous Porphyria**

Although a total plasma porphyrin determination will usually detect EPP and XLP, an erythrocyte protoporphyrin determination is more sensitive. Increases in erythrocyte protoporphyrin occur in many other conditions. Therefore, the diagnosis of EPP must be confirmed by showing a predominant increase in metal-free protoporphyrin rather than zinc protoporphyrin. In XLP, both free and zinc protoporphyrin can be elevated. Interpretation of laboratory reports can be misleading, because the term free erythrocyte protoporphyrin often refers to iron-free protoporphyrin (including zinc protoporphyrin) rather than metal-free protoporphyrin.
Second-Line Testing
More extensive testing is well justified when a first-line test is positive. A substantial increase in PBG may be caused by AIP, HCP, or VP. These acute porphyrias can be distinguished by measuring erythrocyte coproporphyrinogen deaminase (PGBD), urinary porphyrins (using the same spot urine sample), fecal porphyrins, and plasma porphyrins. The various porphyrins that cause blistering skin lesions are differentiated by measuring porphyrins in urine, feces, and plasma. Confirmation at the DNA level is important once the diagnosis is established by biochemical testing.

Testing for Subclinical Porphyria
It is often difficult to diagnose or “rule out” porphyria in patients who had suggestive symptoms months or years in the past, and in relatives of patients with acute porphyrias, because porphyrin precursors and porphyrins may be normal. More extensive testing and consultation with a specialist laboratory and physician may be needed. Before evaluating relatives, the diagnosis of porphyria should be firmly established in an index case, and the laboratory results reviewed to guide the choice of tests for the family members. The index case or another family member with confirmed porphyria should be retested if necessary. Identification of a disease-causing mutation in an index case greatly facilitates detection of additional gene carriers as biochemical tests in latent carriers may be normal.

δ-AMINOLEVULINIC ACID DEHYDRATASE PORPHYRIA
This porphyria is sometimes termed Doss porphyria after the investigator who described the first cases. The term plumboporphyria emphasizes the similarity of this condition to lead poisoning, but incorrectly implies that it is due to lead exposure.

Etiology
This porphyria results from a deficiency of δ-aminolevulinic acid dehydratase (ALAD), which is inherited as an autosomal recessive trait. Only 6 cases have been confirmed by mutation analysis. The prevalence of heterozygous ALAD deficiency was estimated to be <1% in Germany and approximately 2% in Sweden.

Pathology and Pathogenesis
ALAD catalyzes the condensation of 2 molecules of ALA to form the pyrrole PBG (see Fig. 91-1). The enzyme is subject to inhibition by a number of exogenous and endogenous chemicals. ALAD is the principal lead-binding protein in erythrocytes, and lead can displace the zinc atoms of the enzyme. Inhibition of erythrocyte ALAD activity is a sensitive index of lead exposure.

Eleven abnormal ALAD alleles, most with point mutations, have been identified, some expressing partial activity, such that heme synthesis is partially preserved. The amount of residual enzyme activity may predict the phenotypic severity of this disease. Immunochemical studies in 3 cases demonstrated nonfunctional enzyme protein that cross-reacted with anti-ALAD antibodies. Five of the 6 reported ADP cases inherited a different ALAD mutation from each parent. One reported patient with late-onset disease who was heterozygous for a mutant allele developed ADP associated with a myeloproliferative disorder and expansion of an affected clone of erythroid cells.

ADP is often classified as a hepatic porphyria, although the site of overproduction of ALA is not established. A patient with severe, early-onset disease underwent liver transplantation, without significant clinical or biochemical improvement, which might suggest that the excess intermediates did not originate in the liver. Excess urinary coproporphyrin III in ADP might originate from metabolism of ALA to porphyrinogens in a tissue other than the site of ALA overproduction. Administration of large doses of ALA to normal subjects also leads to substantial coproporphyrinuria. Increased erythrocyte protoporphyrin may, as in all other homozygous porphyrrias, be explained by accumulation of earlier pathway intermediates in bone marrow erythroid cells during hemoglobin synthesis, followed by their transformation to protoporphyrin after hemoglobin synthesis is complete. Neurologic symptoms are attributed to neurotoxic effects of ALA, but this is unproven.

Clinical Manifestations
In most cases, symptoms resemble other acute porphyrias, including acute attacks of abdominal pain and neuropathy. Precipitating factors, such as exposure to harmful drugs, have not been evident in most cases. Four of the reported cases were adolescent males. A Swedish infant had more severe disease, with neurologic impairment and failure to thrive. A 63 yr old man in Belgium developed an acute motor polyneuropathy concurrently with a myeloproliferative disorder.

Laboratory Findings
Urinary ALA, coproporphyrin III, and erythrocyte zinc protoporphyrin are substantially increased. Urinary PBG is normal or slightly increased. Erythrocyte ALAD activity is markedly reduced and both parents should have approximately half-normal activity of this enzyme and normal urinary ALA.

Diagnosis and Differential Diagnosis
The 3 other acute porphyrias are characterized by substantial increases in both ALA and PBG. In contrast, ALA but not PBG is substantially increased in ADP. A marked deficiency of erythrocyte ALAD and half-normal activity in the parents support the diagnosis. Other causes of ALAD deficiency, such as lead poisoning, must be excluded. Succinylacetone accumulates in hereditary tyrosinemia type 1 and is structurally similar to ALA, inhibits ALAD, and can cause increased urinary excretion of ALA and clinical manifestations that resemble acute porphyria. Idiopathic acquired ALAD deficiency has been reported. Unlike lead poisoning, the deficient ALAD activity in ADP is not restored by the in vitro addition of sulfhydryl reagents such as dithiothreitol. Even if no other cause of ALAD deficiency is found, it is essential to confirm the diagnosis of ADP by molecular studies.

Treatment
Treatment experience is limited but is similar to other acute porphyrias. Glucose seems not very effective but may be tried for mild symptoms. Hemin therapy was apparently effective for acute attacks in adolescent male cases, and weekly infusions prevented attacks in 2 of these cases. Hemin was not effective either biochemically or clinically in the Swedish child with severe disease, and produced a biochemical response but no clinical improvement in the Belgian man with a late-onset form, who had a peripheral neuropathy but no acute attacks. Hemin is also effective in treating porphyria-like symptoms associated with hereditary tyrosinemia, and can significantly reduce urinary ALA and coproporphyrin in lead poisoning. Avoidance of drugs that are harmful in other acute porphyrias is advisable. Liver transplantation was not effective in the child with severe disease.

Prognosis
The outlook is generally good in typical cases, although recurrent attacks may occur. The course was unfavorable in the Swedish child with more severe disease, and is uncertain in adults with late-onset disease associated with myeloproliferative disorders.

Prevention and Genetic Counseling
Heterozygous parents should be aware that subsequent children are at risk for the disease, as in any autosomal recessive disorder. Prenatal diagnosis is possible, but has not been reported.

ACUTE INTERMITTENT PORPHYRIA
This disorder is also termed pyrroloporphyria, Swedish porphyria, and intermittent acute porphyria and is the most common type of acute porphyria in most countries.

Etiology
AIP results from the deficient activity of the housekeeping form of PBGD. This enzyme is also known as hydroxymethylbilane (HMB)
synthase; the prior term, uroporphyrinogen I synthase, is obsolete. PBGD catalyzes the deamination and head-to-tail condensation of 4 PBG molecules to form the linear tetrapyrrole, HMB (also known as preuroporphyrinogen; see Fig. 91-1). A unique dipyromethene cofactor binds the pyrrole intermediates at the catalytic site until 6 pyroles (including the dipyrrole cofactor) are assembled in a linear fashion, after which the tetrapyrrole HMB is released. The apo-deaminase generates the dipyrrole cofactor to form the holodeaminase, and this occurs more readily from HMB than from PBG. Indeed, high concentrations of PBG may inhibit formation of the holodeaminase. The product HMB can cyclize nonenzymatically to form nonphysiologic uroporphyrinogen I, but in the presence of the next enzyme in the pathway is more rapidly cyclized to form uroporphyrinogen III.

Erythroid and housekeeping forms of the enzyme are encoded by a single gene on human chromosome 11 (11q24.1→q24.2), which contains 15 exons. The 2 isozymes are both monomeric proteins and differ only slightly in molecular weight (approximately 40 and 42 kDa, respectively), and result from alternative splicing of 2 distinct messenger RNA (mRNA) transcripts arising from 2 promoters. The housekeeping promoter functions in all cell types, including erythroid cells.

The pattern of inheritance of AIP is autosomal dominant, with very rare homozygous cases that present in childhood. More than 380 PBGD mutations, including missense, nonsense, and splicing mutations, and insertions and deletions have been identified in AIP, and in many population groups, including blacks. Most mutations are found in only 1 or a few families. But because of founder effects, some are more common in certain geographic areas such as northern Sweden (W198X), Holland (R116W), Argentina (G116R), Nova Scotia (R173W), and Switzerland (W283X). De novo mutations may be found in approximately 3% of cases. Chester porphyria was initially described as a variant form of acute porphyria in a large English family but was found to be caused by a PBGD mutation. The nature of the PBGD mutation does not account for the severity of the clinical presentation, which varies markedly within families.

Most mutations lead to approximately half-normal activity of the housekeeping and erythroid isozymes and half-normal amounts of their respective enzyme proteins in all tissues of heterozygotes. In approximately 5% of unrelated AIP patients, the housekeeping isozyme is deficient, but the erythroid-specific isozyme is normal. Mutations causing this variant are usually found within exon 1 or its 5′ splice donor site or initiation of translation codon. Immunochemical methods can distinguish mutations that are cross-reactive immunologic material (CRIM)–positive (i.e., having excess CRIM relative to the mutant enzyme activity), whereas CRIM-negative mutations either do not synthesize a mutant enzyme protein, or the protein is not stable and not immunologically detectable using anti-PBGD antibodies. A child with homozygous AIP was found to have inherited a different CRIM-positive mutation from each parent.

Pathology and Pathogenesis

Induction of the rate-limiting hepatic enzyme ALAS1 is thought to underlie acute exacerbations of this and the other acute porphyrias. AIP remains latent (or asymptomatic) in the great majority of those who are heterozygous carriers of PBGD mutations, and this is almost always the case before puberty. In those with no history of acute symptoms, porphyrin precursor excretion is usually normal, suggesting that half-normal hepatic PBGD activity is sufficient and hepatic ALAS1 activity is not increased. Many nongenetic factors that lead to clinical expression of AIP, including certain drugs and steroid hormones, have the capacity to induce hepatic ALAS1 and CYPs. Under conditions in which heme synthesis is increased in the liver, half-normal PBGD activity may become limiting and ALA, PBG, and other heme pathway intermediates may accumulate. In addition, heme synthesis becomes impaired and heme-mediated repression of hepatic ALAS1 is less effective.

It is not proven, however, that hepatic PBGD remains constant at approximately 50% of normal activity during exacerbations and remission of AIP, as in erythrocytes. An early report suggested that the enzyme activity is considerably less than half-normal in the liver during an acute attack. Hepatic PBGD activity might be reduced further once AIP becomes activated if, as suggested, excess PBG interferes with assembly of the dihyromethene cofactor for this enzyme. It also seems likely that currently unknown genetic factors play a contributing role in, for example, patients who continue to have attacks even when known precipitants are avoided.

The fact that AIP is almost always latent before puberty suggests that endocrine factors, and especially adult levels of steroid hormones, are important for clinical expression. Symptoms are more common in women suggesting a role for female hormones. Premenstrual attacks are probably the result of endogenous progesterone. Acute porphyrias are sometimes exacerbated by exogenous steroids, including oral contraceptive preparations containing progestins. Surprisingly, pregnancy is usually well tolerated, suggesting that beneficial metabolic changes may ameliorate the effects of high levels of progesterone.

Drugs that are unsafe in acute porphyrias (Table 91-3) include those having the capacity to induce hepatic ALAS1, which is closely associated with induction of CYPs. Some chemicals (e.g., griseofulvin) can increase heme turnover by promoting the destruction of specific CYPs to form an inhibitor (e.g., N-methyl protoporphyrin) of ferrochelatase (FECH, the final enzyme in the pathway). Sulfonamide antibiotics are harmful but apparently not inducers of hepatic heme synthesis. Ethanol and other alcohols are inducers of ALAS1 and some CYPs.

Nutritional factors, principally reduced intake of calories and carbohydrates, as may occur with illness or attempts to lose weight, can increase porphyrin precursor excretion and induce attacks of porphyria. Increased carbohydrate intake may ameliorate attacks. Hepatic ALAS1 is modulated by the peroxisome proliferator-activated receptor γ coactivator-1α, which is an important link between nutritional status and exacerbation of acute porphyria.

Other factors have been implicated. Chemicals in cigarette smoke, such as polycyclic aromatic hydrocarbons, can induce hepatic CYPs and heme synthesis. A survey of AIP patients found an association between smoking and repeated porphyric attacks. Attacks may result from metabolic stress and impaired nutrition associated with major illness, infection, or surgery.

The additive effect of multiple predisposing factors, including drugs, endogenous hormones, nutritional factors, and smoking, is suggested by clinical observations. Exposure to drugs and other precipitating factors is less likely to cause an attack in patients who have had no recent symptoms than in those with recent and frequent porphyric symptoms.

Neurologic Mechanisms

The mechanism of neural damage in acute porphyrias is poorly understood. The most favored hypothesis at present is that 1 or more heme precursors, or perhaps a derivative, are neurotoxic. Increased ALA in AIP, HCP, VP, ADP, plumbism, and hereditary tyrosinemia type 1, which have similar neurologic manifestations, suggests that this substance or a derivative may be neuropathic. Porphyrins derived from ALA after its uptake into cells may have toxic potential. ALA can also interact with γ-aminobutyric acid receptors. Severe AIP improves markedly after allogeneic liver transplantation, which supports the hypothesis that heme precursors from the liver cause the neurologic manifestations.

Epidemiology

AIP occurs in all races and is the most common acute porphyria, with a roughly estimated prevalence in most countries of approximately 5 in 100,000. In Sweden, prevalence was estimated to be 7.7 in 100,000, including latent cases with normal porphyrin precursors. A much higher prevalence of 60-100 in 100,000 in northern Sweden is the result of a founder effect. The combined prevalence of AIP and VP in Finland is approximately 3.4 in 100,000. A survey of chronic psychiatric patients in the United States using an erythrocyte PBGD determination found a high prevalence (210 in 100,000) of PBGD deficiency, but a study in Mexico found a similar prevalence in psychiatric patients and controls. Population screening by erythrocyte PBGD activity or DNA analysis revealed a prevalence of 200 heterozygotes per 100,000.
In affected heterozygotes, acute attacks are characterized by a constellation of nonspecific symptoms, which may become severe and life-threatening. Abdominal pain occurs in 85-95% of cases, is usually severe, steady, and poorly localized, but sometimes cramping, and accompanied by signs of ileus, including abdominal distention and decreased bowel sounds. Nausea, vomiting, and constipation are common, but increased bowel sounds and diarrhea may occur. Bladder dysfunction may cause hesitancy and dysuria. Tachycardia, the most common physical sign, occurs in up to 80% of attacks. This is often accompanied by hypertension, restlessness, coarse or fine tremors, and excess sweating, which are attributed to sympathetic overactivity and increased catecholamines. Other common manifestations include mental symptoms; pain in the extremities, head, neck, or chest; muscle weakness; and sensory loss. Because all these manifestations are neurologic rather than inflammatory, there is little or no abdominal tenderness, fever, or leukocytosis.

Porphyric neuropathy is primarily motor and appears to result from axonal degeneration rather than demyelination. Sensory involvement is indicated by pain in the extremities, which may be described as muscle or bone pain, and by numbness, paresthesias, and dysesthesias. Paresis may occur early in an attack, but is more often a late manifestation in an attack that is not recognized and adequately treated. Rarely, severe neuropathy develops when there is little or no abdominal pain. Motor weakness most commonly begins in the proximal muscles of the upper extremities and then progresses to the lower extremities and the periphery. It is usually symmetric, but occasionally asymmetric or focal. Initially, tendon reflexes may be little affected or hyperactive and become decreased or absent. Cranial nerves, most commonly X and VII, may be affected, and blindness from involvement of the optic nerves or occipital lobes has been reported. More common central nervous system manifestations include seizures, anxiety, insomnia, depression, disorientation, hallucinations, and paranoia. Seizures may result from hypotension, porphyria itself, or an unrelated cause. Chronic depression and other mental symptoms occur in some patients, but attribution to porphyria is often difficult.

Hypotension is common during acute attacks. Inappropriate antidiuretic hormone secretion is often the most likely mechanism, but salt depletion from excess renal sodium loss, gastrointestinal loss, and poor intake have been suggested as causes of hypotension in some patients. Unexplained reductions in total blood and red blood cell volumes are sometimes found, and increased antidiuretic hormone secretion might then be an appropriate physiologic response. Other electrolyte abnormalities may include hypomagnesemia and hypercalcaemia.

The attack usually resolves within several days, unless treatment is delayed. Abdominal pain may resolve within a few hours and paresis within a few days. Even severe motor neuropathy can improve over months or several years, but may leave some residual weakness. Progression of neuropathy to respiratory and bulbar paralysis and death is uncommon with appropriate treatment and removal of harmful drugs. Sudden death may result from cardiac arrhythmia.

**Laboratory Findings**

Levels of ALA and PBG are substantially increased during acute attacks and these may decrease after an attack but usually remain increased unless the disease becomes asymptomatic for a prolonged period. A population-based study in Sweden indicated that symptoms suggestive of porphyria may occur in heterozygotes during childhood, in contrast to adults, even when urinary porphyrin precursors are not elevated. This study lacked a comparison with the frequency of such nonspecific symptoms in a control group of children.

Porphyrins are also markedly increased, which accounts for reddish urine in AIP. These are predominantly uroporphyrins, which can form nonenzymatically from PBG. But because the increased urinary porphyrins in AIP are predominantly isomer III, their formation is likely to be largely enzymatic, which might occur if excess ALA produced in the liver enters cells in other tissues and is then converted to porphyrins via the heme biosynthetic pathway. Porphobilin, a degradation product of PBG, and dipyrrolymethenes appear to account for brownish

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Table 91-3  Drugs Regarded as Unsafe and Safe in Acute Porphyrias

<table>
<thead>
<tr>
<th>UNSAFE</th>
<th>SAFE</th>
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<tbody>
<tr>
<td>Barbiturates</td>
<td>Narcotic analgesics</td>
</tr>
<tr>
<td>Sulfonamide antibiotics*</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Meprobamate* (also mebutamate, tybamate*)</td>
<td>Acetaminophen</td>
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<tr>
<td>Carisoprodol*</td>
<td>Phenothiazines</td>
</tr>
<tr>
<td>Glutethimide*</td>
<td>Penicillin and derivatives</td>
</tr>
<tr>
<td>Methyprylon</td>
<td>Streptomycin</td>
</tr>
<tr>
<td>Ethchlorvynol*</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Mephenytoin</td>
<td>Bromides</td>
</tr>
<tr>
<td>Phenytoin*</td>
<td>Insulin</td>
</tr>
<tr>
<td>Succinimides</td>
<td>Atropine</td>
</tr>
<tr>
<td>Carbamazepine*</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Clonazepam†</td>
<td>Ranitidine†</td>
</tr>
<tr>
<td>Primidon*</td>
<td>Acetaminophen (paracetamol)</td>
</tr>
<tr>
<td>Valproic acid*</td>
<td>Acetazolamide</td>
</tr>
<tr>
<td>Pyrazolones (aminopyrine, antipyrine)</td>
<td>Allopurinol</td>
</tr>
<tr>
<td>Griseofulvin*</td>
<td>Amiloride</td>
</tr>
<tr>
<td>Ergots</td>
<td>Bethanidine</td>
</tr>
<tr>
<td>Metoclopramide*‡</td>
<td>Burometanide</td>
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<tr>
<td>Rifampin*</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Pyrazinamide*‡</td>
<td>Coumarins</td>
</tr>
<tr>
<td>Diclofenac*‡</td>
<td>Flurbiprofen</td>
</tr>
<tr>
<td>Progesterone and synthetic progestins*</td>
<td>Gabapentin</td>
</tr>
<tr>
<td>Danazol*</td>
<td>Gentamicin</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Guanethidine</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors (especially enalapril)†</td>
<td>Ofoxacin</td>
</tr>
<tr>
<td>Calcium channel blockers (especially nifedipine)‡</td>
<td>Propranolol</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Succinylcholine</td>
</tr>
<tr>
<td>Tetracycline</td>
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</tbody>
</table>

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This partial listing does not include all available information about drug safety in acute porphyrrias. Other sources should be consulted for drugs not listed here.

*Porphyria has been listed as a contraindication, warning, precaution, or adverse effect in U.S. labeling for these drugs. Estrogens are also listed as harmful in porphyria, but have been implicated as harmful in acute porphyrrias mostly based only on experience with estrogen-progestin combinations. Although estrogens can exacerbate PCT, there is little evidence they are harmful in the acute porphyrrias.

†Porphyria has been listed as a precaution in U.S. labeling for this drug. However, this drug is regarded as safe by other sources.

‡These drugs have been classified as probably safe by some sources, but this is controversial and they should be avoided.

people in Finland, and 1 in approximately 1,675 (60 in 100,000 people) in France. Therefore, carriers of PBGD mutations that can cause AIP may be common.

**Clinical Manifestations**

Neurovisceral manifestations of acute porphyrrias may appear any time after puberty, but rarely before. Very rare cases of homozygous AIP develop severe neurologic manifestations early in childhood.
The chloride is replaced by the hydroxyl ion, forming hydroxyheme, or hematin. Protoporphyrin IX, and is usually isolated as hemin chloride. In alkaline solution, the compound is less sensitive when renal function is normal. Measurement of urine ALA and urine porphyrins or porphyrin precursors. Few patients who have increased porphyrins or porphyrin precursors. Few patients who are asymptomatic individuals who have increased porphyrins or porphyrin precursors. Few patients who have developed this neoplasm have had increases in serum α-fetoprotein. Patients with acute porphyrias, especially older than age 50 yr must be screened at least yearly by ultrasound or an alternative imaging method.

The risk of chronic hypertension and impaired renal function, most often with evidence of interstitial nephritis, is increased in AIP. A nephrotoxic effect of ALA may contribute. This may progress to severe renal failure and require renal transplantation.

Increased serum thyroxin levels because of increased thyroxin-binding globulin occur in some AIP patients. Hypercholesterolemia and elevated low-density lipoprotein cholesterol appear to be less common in this disorder than previously thought.

## Treatment

### Hemin

Intravenous hemin, combined with symptomatic and supportive measures, is the treatment of choice for most acute attacks of porphyria. There is a favorable biochemical and clinical response to early treatment with hemin, but less rapid clinical improvement if treatment is delayed. It is no longer recommended that therapy be started only after an unsuccessful trial of intravenous glucose for several days. Mild attacks, without severe manifestations such as paresis and hyponatremia, may be treated initially with intravenous glucose. After intravenous administration, hemin binds to hemopexin and albumin in plasma and is taken up primarily in hepatocytes. Hemin then enters and augments the regulatory heme pool in erythrocytes, represses the synthesis of hepatic ALAS1, and dramatically reduces porphyrin precursor overproduction.

Hemin* is available for IV administration in the United States as a lyophilized hematin preparation (Panhematin, Recordati). Degradation products begin to form as soon as the lyophilized product is reconstituted with sterile water, and these are responsible for phlebitis at the site of infusion and a transient anticoagulant effect. Loss of venous access due to phlebitis is common after repeated administration. Stabilization of lyophilized hematin by reconstitution with 30% human albumin can prevent these adverse effects, and is recommended, especially if a peripheral vein is used for the infusion. Uncommon side effects of hemin include fever, aching, malaise, hemoysis, anaphylaxis, and circulatory collapse. Heme arginate, a more stable hemin preparation, is available in Europe and South Africa.

Hemin treatment should be instituted only after a diagnosis of acute porphyria has been initially confirmed by a marked increase in urinary PBG (determined most rapidly using a kit). When prior documentation of the diagnosis is available for review, it is not essential to confirm an increase in PBG with every recurrent attack, if other causes of the symptoms are excluded clinically. The standard regimen of hemin for treatment of acute porphyrinic attacks is 3–4 mg/kg daily for 4 days. Lower doses have less effect on porphyrin precursor excretion and probably less clinical benefit.

### General and Supportive Measures

Drugs that may exacerbate porphyrias (see Table 91-3) should be discontinued whenever possible, and other precipitating factors identified. Hospitalization is warranted, except for mild attacks, for treatment of severe pain, nausea, and vomiting; for administration of hemin and fluids; and for monitoring vital capacity, nutritional status, neurologic function, and electrolytes. Pain usually requires a narcotic analgesic; there is low risk for addiction after recovery from the acute attack. Ondansetron or a phenothiazine such as chlorpromazine is needed for nausea, vomiting, anxiety, and restless. Chloral hydrate or low doses of short-acting benzodiazepines can be given for restless or insomnia. β-Adrenergic blocking agents may be useful during acute attacks to control tachycardia and hypertension, but may be hazardous in patients with hypovolemia and incipient cardiac failure.

### Carbohydrate Loading

The effects of carbohydrates on repressing hepatic ALAS1 and reducing porphyrin precursor excretion are weak compared to those of hemin. Therefore, only mild attacks (mild pain, no paresis or hyponatremia) are treated with carbohydrate loading. Glucose polymer solutions by mouth are sometimes tolerated. At least 300 g of intravenous glucose, usually given as a 10% solution, has been recommended for adults hospitalized with attacks of porphyria. Amounts up to 500 g daily may be more effective, but large volumes may favor development of hyponatremia.

### Other Therapies

Liver transplantation was effective in several patients with severe AIP. A group from the United Kingdom reported their experience with liver transplantation in 10 AIP patients with significantly impaired quality of life and recurrent attacks which were refractory to medical management. Patients had a complete biochemical and symptomatic resolution posttransplantation; 2 patients in this series, however, succumbed to multiorgan failure posttransplantation. Liver transplantation is a high-risk procedure and should be considered as a last resort in patients with severe recurrent attacks that are refractory to other treatment. Cimetidine, a well-known inhibitor of hepatic CYPs, can prevent experimental forms of porphyria induced by chemical agents that undergo activation by these enzymes, but these models are not highly relevant to human AIP. The drug’s use is based on uncontrolled observations.

### Seizures and Other Complications

Seizures caused by hyponatremia or other electrolyte imbalances may not require prolonged treatment with anticonvulsant drugs, most of which have at least some potential for exacerbating acute porphyrrias. Bromides, gabapentin, and probably vigabatrin are safe. Clonazepam may be less harmful than phenytoin or barbiturates. Control of hypertension may help prevent chronic renal impairment, which can progress and require renal transplantation.

### Safe and Unsafe Drugs

Patients often do well with avoidance of harmful drugs. Table 91-3 lists some drugs known or strongly suspected to be harmful or safe in the treatment of acute porphyria.
acute porphyrias. More extensive listings are available on websites of the European Porphyria Network (www.porphyria-europe.com) and the American Porphyria Foundation (www.porphyriafoundation.com), but some listings are controversial. Information regarding safety is lacking for many drugs, especially for those recently introduced.

Exogenous progestins, usually in combination with estrogens, can induce attacks of porphyria. Estrogens are seldom reported to be harmful when given alone or in animal and hepatocyte culture systems. Synthetic steroids with an ethinyl substituent can cause a mechanism-based destruction of hepatic CYPs and should probably be avoided in patients with acute porphyria. Danazol is especially contraindicated.

Other Situations
Major surgery can be carried out safely in patients with acute porphyria, especially if barbiturates are avoided. Halothane has been recommended as an inhalation agent and propofol and midazolam as intravenous induction agents.

Pregnancy is usually well tolerated, which is surprising, because levels of progesterone, a potent inducer of hepatic ALAS1, are considerably increased during pregnancy. Some women do experience continuing attacks during pregnancy. This has sometimes been attributed to reduced caloric intake or metoclopramide, a drug sometimes used to treat hyperemesis gravidarum and considered harmful in acute porphyrias.

Diabetes mellitus and other endocrine conditions are not known to precipitate attacks of porphyria. In fact, the onset of diabetes mellitus and resulting high circulating glucose levels may decrease the frequency of attacks and lower porphyrin precursor levels in AIP.

Prognosis
The outlook for patients with acute porphyrias has improved markedly in the past several decades. In Finland, for example, 74% of patients with AIP or VP reported that they led normal lives, and <30% had recurrent attacks during several years of follow-up. In those presenting with acute symptoms, recurrent attacks were most likely within the next 1-3 yr. Moreover, only 6% of gene carriers who had never had attacks developed symptoms. The improved outlook may result from earlier detection, better treatment of acute attacks, and replacement of harmful drugs such as barbiturates and sulfonamides with safer drugs. Some patients continue to have recurrent attacks, chronic pain, and other symptoms even after avoiding known exacerbating factors.

Prevention
For prevention of attacks, it is important to identify multiple inciting factors and remove as many as possible. Drugs for concurrent medical conditions should be reviewed. Because dietary factors are often inapparent, consultation with a dietitian may be useful. A well-balanced diet that is somewhat high in carbohydrate (60-70% of total calories) and sufficient to maintain weight is recommended. There is little evidence that additional dietary carbohydrate helps further in preventing attacks, and it may lead to weight gain. Patients who wish to lose excess weight should do so gradually and when they are clinically stable. Rapid weight loss after bariatric surgery may exacerbate acute porphyrias. Iron deficiency, which can be detected by a low serum ferritin, should be corrected.

Gonadotropin-releasing hormone analogs, which reversibly suppress ovulation, can be dramatically effective for preventing frequently recurring luteal phase attacks, but baseline and continuing gynecologic evaluation and bone density measurements are important, and transdermal estrogen or a bispophonate may be added to prevent bone loss. Hemin administered once or twice weekly can prevent frequent, noncyclic attacks of porphryia in some patients.

Genetic Counseling
Children with a family history of porphyria are often seen by pediatricians for evaluation and counseling. Information and laboratory results from a relative with proven porphyria must be reviewed in order to guide testing of the child, which is different depending on the type of acute porphyria. A mutation identified in the index case can be sought in the child. If the child is found to have inherited the mutation, counseling to avoid potentially harmful drugs is appropriate. Counseling should also emphasize that the great majority of those who inherit a PBGD mutation never develop symptoms, and the prognosis of those who do is favorable. Therefore, a normal, healthy life is expected, especially with avoidance of harmful drugs and other factors and prompt recognition and treatment of symptoms should they occur. Given the favorable outlook for most mutation carriers, even during pregnancy, having children is not precluded, and prenatal diagnosis of acute porphyrias is less important than it is for many other inherited diseases.

CONGENITAL ERYTHROPOIETIC PORPHYRIA
Also termed Günther disease, this rare disease usually presents with photosensitivity shortly after birth or in utero as nonimmune hydrops.

Etiology
CEP is an autosomal recessive disease caused by a marked deficiency of uroporphyrinogen III synthase (UROS). Many UROS mutations have been identified among CEP families. Later-onset disease in adults is likely to be associated with myeloproliferative disorders and expansion of a clone of erythroblasts that carry a UROS mutation.

Pathology and Pathogenesis
UROS, which is markedly deficient in CEP, catalyzes inversion of pyrrole ring D of HMB (the pyrrole ring shown on the right end of the molecule in Fig. 91-1) and rapid cyclization of the linear tetrapyrole to form uroporphyrinogen III. This enzyme is also termed uroporphyrinogen III cosynthase. The human enzyme is a monomer. The gene for the enzyme is found on chromosome 1q25.3-→q26.3, and contains 10 exons. Erythroid and housekeeping transcripts are generated by alternative promoters but encode the same enzyme.

In CEP, HMB accumulates in erythroid cells during hemoglobin synthesis and cyclizes nonenzymatically to form uroporphyrinogen I, which is auto-oxidized to uroporphyrin I. Some of the uroporphyrinogen I that accumulates is metabolized to coproporphyrinogen I, which accumulates because it is not a substrate for coproporphyrinogen oxidase. Thus, both uroporphyrin I and coproporphyrin I accumulate in the bone marrow and are then found in circulating erythrocytes, plasma, urine, and feces. A variety of UROS mutations have been identified in CEP, including missense and nonsense mutations, large and small deletions and insertions, splicing defects, and intronic branch point mutations. At least 4 mutations have been identified in the erythroid-specific promoter. Many patients inherited a different mutation from each parent, and most mutations have been detected in only 1 or a few families. An exception is a common mutation, C73R, which is at a mutational hotspot and was found in ~33% of alleles. One child with CEP had a GATA1 mutation, with no UROS mutation. The CEP phenotype may be modulated by gain of function ALAS2 mutations, which were first identified as causing XLP.

Genotype–phenotype correlations have been based on the in vitro expression of various CEP mutations and the severity of associated phenotypic manifestations. The C73R allele, which is associated with a severe phenotype in homozygotes or in patients heteroallelic for C73R and another mutation expressing little residual activity, resulted in <1% of normal enzyme activity. Patients with the C73R allele and heteroallelic for other mutations expressing more residual activity have milder disease.

Hemolysis is a common feature of CEP. Excess porphyrins in circulating erythrocytes cause cell damage, perhaps by a phototoxic mechanism, leading to both intravascular hemolysis and increased splenic clearance of erythrocytes. Also important is ineffective erythropoiesis, with intramedullary destruction of porphyrin-laden erythroid cells and breakdown of heme. Expansion of the bone marrow as a result of erythroid hyperplasia may contribute to bone loss. Nutrient deficiencies sometimes cause erythroid hypoplasia. Despite the marked deficiency of UROS, heme production in the bone marrow is increased because of hemolysis and a compensatory increase in hemoglobin
Clinical Manifestations

In severe cases, CEP can cause fetal loss, or be recognized in utero as intrauterine hemolytic anemia and nonimmune hydrops fetalis. CEP may be associated with neonatal hyperbilirubinemia, and phototherapy may unintentionally induce severe photosensitivity and scarring.

The most characteristic presentation is reddish urine or pink staining of diapers by urine or meconium shortly after birth (Fig. 91-2). With sun exposure, severe blistering lesions appear on exposed areas of skin on the face and hands, and have been termed hydroa aestivale because they are more severe with greater sunlight exposure during summer (Fig. 91-3). Vesicles and bullae, as well as friability, hypertrichosis, scarring, thickening, and areas of hypopigmentation and hyperpigmentation are very similar to those seen in PCT but usually much more severe. Infection and scarring sometimes cause loss of facial features and fingers and damage to the cornea, ears, and nails. Porphyrins are deposited in dentine and bone in utero. Reddish-brown teeth in normal light, an appearance termed erythrodontia, display reddish fluorescence under long-wave UV light (Fig. 91-4). Unaffected children born to a mother with CEP may have erythrodontia. Hemolysis and splenomegaly appear in CEP. Bone marrow compensation may be adequate, especially in milder cases. Patients with severe phenotypes, however, are often transfusion-dependent. Splenomegaly may contribute to the anemia and cause leukopenia and thrombocytopenia, which may be complicated by significant bleeding. Neuropathic symptoms are absent, and there is no sensitivity to drugs, hormones, and carbohydrate restriction. The liver may be damaged by iron overload or viral hepatitis acquired from blood transfusions.

Milder cases of CEP with onset of symptoms in adult life and without erythrodontia may mimic PCT. These late-onset cases are likely to be associated with myeloproliferative disorders, and expansion of a clone of cells carrying a UROS mutation.

Laboratory Findings

Urinary porphyrin excretion and circulating porphyrin levels in CEP are much higher than in almost all other porphyrias. Urinary porphyrin excretion can be as high as 50-100 mg daily, and consists mostly of uroporphyrin I and coproporphyrin I. ALA and PBG are normal. Fecal porphyrins are markedly increased, with a predominance of coproporphyrin I.

Figure 91-2 Congenital erythropoietic porphyria. The diaper of an affected baby demonstrates the red color of urine. (From Paller AS, Macini AJ: Hurwitz clinical pediatric dermatology, ed 3, Philadelphia, 2006, Elsevier Saunders, p. 517.)

Figure 91-3 Congenital erythropoietic porphyria. Vesicles, bullae, and crusts on sun-exposed areas. (From Paller AS, Macini AJ: Hurwitz clinical pediatric dermatology, ed 3, Philadelphia, 2006, Elsevier Saunders, p. 517.)

Figure 91-4 Congenital erythropoietic porphyria. Brownish teeth that fluoresce under Wood lamp examination. (From Paller AS, Macini AJ: Hurwitz clinical pediatric dermatology, ed 3, Philadelphia, 2006, Elsevier Saunders, p. 517.)

Marked increases in erythrocyte porphyrins in CEP consist mostly of uroporphyrin I and coproporphyrin I. These porphyrins are also increased in bone marrow, spleen, plasma, and, to a lesser extent, liver. The porphyrin pattern in erythrocytes is influenced by rates of erythropoiesis and erythroid maturation. A predominance of protoporphyrin has been noted in some CEP patients, and in 1 such patient, uroporphyrin and coproporphyrin increased when erythropoiesis was stimulated by blood removal.

Diagnosis and Differential Diagnosis

The diagnosis of CEP should be documented by full characterization of porphyrin patterns and identification of the underlying mutations. In later-onset cases, an underlying myeloproliferative disorder and a UROS somatic mutation should be suspected and studied in detail.

The clinical picture in hepatoerythropoietic porphyria (HEP) may be very similar, but the porphyrin patterns in urine and feces in HEP resemble PCT. A predominant increase in erythrocyte protoporphyrin is unusual in CEP but is characteristic of HEP, and rare homozygous cases of AIP, HCP, and VP. EPP is also distinguished by normal urinary porphyrins and by increases in erythrocyte metal-free protoporphyrin, whereas the increased protoporphyrin in other conditions is complexed with zinc.

CEP should be suspected as a cause of nonimmune hydrops or hemolytic anemia in utero. With recognition of the disease at this stage, intrauterine transfusion can be considered, and severe, scarring photosensitivity from phototherapy for hyperbilirubinemia avoided. Prenatal diagnosis is feasible by finding red-brown discoloration and increased porphyrins in amniotic fluid, and measuring porphyrins in fetal erythrocytes and plasma. UROS activity can be measured in cultured amniotic fluid cells, or UROS mutations identified in chorionic villi or cultured amniotic cells.
**Treatment**

Protection from sunlight exposure, minimizing skin trauma, and prompt treatment of any cutaneous infections are highly important in managing CEP. Sunscreen lotions and beta-carotene are sometimes beneficial. Transfusions to achieve a level of hemoglobin sufficient to suppress erythropoiesis significantly can be quite effective in reducing porphyrin levels and photosensitivity. Concurrent deferoxamine to reduce iron overload, and hydroxyurea to suppress erythropoiesis further may provide additional benefit. Splenectomy reduces hemolysis and transfusion requirements in some patients. Oral charcoal may increase fecal loss of porphyrins, but may contribute little in more severe cases. Intravenous hemin may be somewhat effective, but has not been extensively studied and seems unlikely to provide long-term benefit.

The most effective treatment is bone marrow or stem cell transplantation in early childhood, which has markedly reduced porphyrin levels and photosensitivity and increased long-term survival.

**Prognosis**

The outlook is favorable in milder cases and in patients with more severe disease especially after successful bone marrow or stem cell transplantation.

**Prevention and Genetic Counseling**

Genetic counseling is important for affected families, because CEP can be recognized before birth and a severe phenotype can often be predicted by identifying the nature of the UROS mutations.

**PORPHYRIA CUTANEA TARDA**

PCT is the most common and readily treated human porphyria (see Table 91-2). It occurs in mid or late adult life, and is rare in children. Previous terms include symptomatic porphyria, PCT symptomatica, and idiosyncratic porphyria. The underlying cause is a liver-specific, acquired deficiency of uroporphyrinogen decarboxylase (UROD) with contributions by several types of genetic and acquired factors. Heterozygous UROD mutations are found in familial PCT. HEP, the homozygous form of familial PCT, usually has a more severe presentation in childhood, resembling CEP clinically.

**Etiology**

PCT is caused by a reduction of hepatic UROD activity to 20% of normal activity or less. An inhibitor of hepatic UROD has been characterized as uroporphomethene, which is derived from partial oxidation of the enzyme substrate uroporphyrinogen. CYPs, such as CYP1A2, as well as iron, are involved in its formation (Fig. 91-5). Although enzyme activity is inhibited, the amount of hepatic enzyme protein measured immunologically remains at its genetically determined level.

UROD catalyzes the decarboxylation of the 4 acetic acid side chains of uroporphyrinogen (an octacarboxyl porphyrinogen) to form coproporphyrinogen (a tetracarboxyl porphyrinogen) (see Fig. 91-1). The enzyme reaction occurs in a sequential, clockwise fashion, with the intermediate formation of hepta-, hexa-, and pentacarboxyl porphyrinogens. Uroporphyrinogen III, as compared with other uroporphyrinogen isomers, is the preferred substrate. Human UROD is a dimer with the 2 active site clefts juxtaposed. The UROD gene is on chromosome 1p34 and contains 10 exons, with only 1 promoter. Therefore, the gene is transcribed as a single mRNA in all tissues.

The majority of PCT patients (i.e., ~80%) have no UROD mutations and are said to have sporadic (type 1) disease. Some are heterozygous for UROD mutations and are said to have familial (type 2) PCT. Described mutations include missense, nonsense, and splice-site mutations, several small and large deletions, and small insertions, with only a few identified in more than 1 family. A few of these mutations may be located near the active site cleft, but most appear to involve regions with important structural roles. Being heterozygous for a UROD mutation is insufficient to cause PCT unless a UROD inhibitor is also generated. Because penetrance of the genetic trait is low, many patients with familial PCT have no family history of the disease.

Induction of hepatic ALAS1 is not a prominent feature in PCT, although alcohol may increase this enzyme slightly. Iron and estrogens are also not potent inducers of ALAS1 and drugs that are potent inducers of ALAS1 and CYPs are much less commonly implicated in PCT than in acute porphyrias.

Blistering skin lesions result from porphyrins that are released from the liver. Sunlight exposure leads to generation of reactive oxygen species in the skin, complement activation, and lysosomal damage.

**Epidemiology**

Differences in prevalence probably relate to geographic variations in susceptibility factors such as hepatitis C and ethanol use. The yearly incidence in the United Kingdom was estimated at 2-5 in 1,000,000 in the general population, and the prevalence in the United States and Czechoslovakia was estimated at approximately 1 in 25,000 and 1 in 5,000 in the general population, respectively. The disease was reported to be prevalent in the Bantus of South Africa in association with iron overload. PCT is more common in males, possible because of greater alcohol intake, and in women it is commonly associated with estrogen use.

A massive outbreak of PCT occurred in eastern Turkey in the 1950s. Wheat intended for planting and treated with hexachlorobenzene as a fungicide was consumed by many at a time of food shortage. Cases and small outbreaks of PCT after exposure to other chemicals including di- and trichlorophenols and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, dioxin) have been reported. The manifestations improved in most cases when the exposure was stopped. There are reported cases of delayed onset many years after chemical exposure.

**Pathology and Pathogenesis**

PCT is currently classified into 3 clinically similar types. Generation of a UROD inhibitor in the liver plays an important role in all 3 types. The 80% of patients with type 1 (sporadic) PCT have no UROD mutations, and UROD activity is normal in nonhepatic tissues such as erythrocytes. In familial (type 2) PCT, a heterozygous UROD mutation results in a partial (approximately 50%) deficiency of UROD in all tissues from birth, and the disease becomes active in some heterozygotes when other susceptibility factors are present and a UROD inhibitor is generated in the liver, reducing hepatic UROD activity to 20% of normal or less. HEP results from inheritance of a UROD mutation from each parent and typically cause severe photosensitivity resembling CEP starting in early childhood. Some compound heterozygotes have developed symptoms in childhood more typical of PCT. Type 3 is rare, and describes PCT with normal erythrocyte UROD activity occurring in more than 1 family member. Another genetic basis, such as HFE mutations, may be identified in type 3.

CYPs, especially CYP1A2, can catalyze the oxidation of uroporphyrinogen I to uroporphyrin. This uroporphyrinogen oxidase activity is
enhanced by iron, and leads to formation of a UROD inhibitor (see Fig. 91-5). CYP1a2 seems essential for development of uroporphyria in rodents, because experimental uroporphyria does not develop in CYP1a2 knockout mice.

**Susceptibility Factors**

The following factors are implicated in the development of PCT, and these occur in various combinations in individual patients.

**Iron**

A normal or increased amount of iron in the liver is essential for developing PCT, and treatment by phlebotomy to reduce hepatic iron leads to remission. Serum ferritin levels are usually in the upper part of the normal range or moderately increased and liver histology commonly shows increased iron staining. Prevalence of the C282Y mutation of the HFE gene, which is the major cause of hemochromatosis in people of northern European ancestry, is increased in both type 1 and type 2 PCT, and approximately 10% of patients are C282Y homozygotes. In southern Europe, the H63D mutation is more commonly associated. PCT may develop in patients with secondary iron overload. Reduced hepatic expression of the hormone hepcidin occurs in hemochromatosis and also in PCT, regardless of HFE genotype, which may explain hepatic siderosis in this condition.

**Hepatitis C**

This viral infection is highly prevalent in PCT in most geographic locations; in the United States, for example, it is present in 56-74% of cases, which is similar to rates in southern Europe. Prevalence of hepatitis C in PCT is lower in northern Europe (<20%). Steatosis and oxidative stress in hepatitis C may favor iron-mediated generation of reactive oxygen species and a UROD inhibitor. Dysregulation of hepcidin occurs in hepatitis C and may lead to increased iron absorption.

**HIV**

Many reports suggest that HIV infection can contribute to the development of PCT, although less commonly than does hepatitis C.

**Ethanol**

The long-recognized association between alcohol and PCT may be explained by the generation of active oxygen species, which may cause oxidative damage, mitochondrial injury, depletion of reduced glutathione and other antioxidant defenses, increased production of endotoxin, and activation of Kupffer cells. Alcohol may contribute to iron overload by impairing hepcidin production.

**Smoking and Cytochrome P450 Enzymes**

Smoking has not been extensively studied as a susceptibility factor but is commonly associated with alcohol use in PCT. It may act to induce hepatic CYPs and oxidative stress. Hepatic CYPs are thought to be important in oxidizing uroporphyrinogen and generating a UROD inhibitor (see Fig. 91-5). Genetic polymorphisms of CYP1A2 and 1A1 have been implicated in human PCT. The frequency of an inducible CYP1A2 genotype was more common in PCT patients than in controls in several studies.

**Antioxidant Status**

Ascorbic acid deficiency contributes to uroporphyria in laboratory models and perhaps in human PCT. In 1 series, plasma ascorbate levels were substantially reduced in 84% of patients with PCT. Low levels of serum carotenoids were also described, further suggesting that oxidant stress in hepatocytes is important in PCT.

**Estrogens**

Use of estrogen-containing oral contraceptives or postmenopausal estrogen replacement is very commonly associated with PCT (type 1 or 2) in women. PCT sometimes occurs during pregnancy, although it is not clear whether the risk is increased.

**Clinical Manifestations**

**Cutaneous Manifestations**

PCT is readily recognized by blistering and crusted skin lesions on the backs of the hands, which are the most sun-exposed areas of the body, and somewhat less commonly on the forearms, face, ears, neck, legs, and feet. The fluid-filled vesicles commonly rupture and become crusted or denuded areas, heal slowly, and are subject to infection. The skin on the backs of the hands is characteristically friable, and minor trauma may cause blisters or denudation of skin. Small white plaques, termed milia, may precede or follow vesicle formation. Facial hypertrichosis and hyperpigmentation are also common. Severe scarring and thickening of sun-exposed skin may resemble scleroderma. Skin biopsy findings include subepidermal blistering and deposition of periodic acid–Schiff-positive material around blood vessels and fine fibrillar material at the dermoepithelial junction, which may relate to excessive skin fragility. Immunoglobulin G, other immunoglobulins, and complement are also deposited at the dermoepithelial junction and around dermal blood vessels. The skin lesions and histologic changes are not specific for PCT. The same findings occur in VP and HCP, and resemble those of CEP and HEP, but are usually less severe. PCT usually develops in mid or late adult life. Earlier onset may be seen in those with UROD or HFE mutations. Childhood onset is rare, and suggests heterozygosity or even compound heterozygosity for UROD mutations.

**Liver Abnormalities**

PCT is almost always associated with nonspecific liver abnormalities, especially increased serum transaminases and γ-glutamyltranspeptidase, even in the absence of heavy alcohol intake or hepatitis C. Most histologic findings, such as necrosis, inflammation, increased iron, and increased fat, are nonspecific. Specific findings include red fluorescence of liver tissue, and fluorescent, birefringent, needle-like inclusions presumably consisting of porphyrins. Electron microscopy shows these inclusions are in lysosomes, and paracrystalline inclusions are found in mitochondria. Distorted lobular architecture and cirrhosis are more common with long-standing disease.

The risk of developing hepatocellular carcinoma is increased, with reported incidences ranging from 4-47% in PCT. These tumors seldom contain large amounts of porphyrins.

**Other Findings and Associations**

Mild or moderate erythrocytosis in some adult patients is not well understood, but chronic lung disease from smoking may contribute. An earlier onset of symptoms may be noted in patients with genetic predisposing factors, such as an inherited partial deficiency of UROD or the C282Y/C282Y HFE genotype. Iron overload secondary to conditions such as myelofibrosis and end-stage renal disease may be associated with PCT. The disease can be especially severe in patients with end-stage renal disease, because the lack of urinary excretion leads to much higher concentrations of porphyrins in plasma, and the excess porphyrins are poorly dialyzable. PCT occurs more frequently in patients with systemic lupus erythematosus and other immunologic disorders than would have been expected by chance.

**Laboratory Findings**

Porphyrins accumulate in the liver mostly as the oxidized porphyrins rather than porphyrinogens in PCT, as indicated by the immediate red fluorescence observed in liver tissue. This develops over weeks or months before porphyrins appear in plasma and are transported to the skin, causing photosensitivity. In contrast to the acute hepatic porphyrias, only a very small increase in synthesis of heme pathway intermediates presumably consisting of porphyrins. Electron microscopy shows these inclusions are in lysosomes, and paracrystalline inclusions are found in mitochondria. Distorted lobular architecture and cirrhosis are more common with long-standing disease.
urine, with lesser amounts of coproporphyrin and penta- and hexacarboxyl porphyrin. A normally minor pathway is accentuated by UROD deficiency, whereby pentacarboxyl porphyrinogen is oxidized by coproporphyrinogen oxidase (CPOX; the next enzyme in the pathway), forming isocoprotoporphyrinogen, an atypical tetracarboxyl porphyrinogen. Relative to normal values, urinary porphyrins are increased to a greater extent than fecal porphyrins. However, the total amount of porphyrins excreted in feces in PCT exceeds that in urine, and total excretion of type III isomers (including isocoprotoporphyrins, which are mostly derived from the type III series) exceeds that of type I isomers. Perhaps because uroporphyrinogen III is the preferred substrate for UROD, more uroporphyrinogen I than III accumulates and is excreted in PCT. Hepta- and hexacarboxyl porphyrin are mostly isomer III; and pentacarboxyl porphyrin and coproporphyrin are approximately equal mixtures of isomers I and III.

**Diagnosis and Differential Diagnosis**

Plasma porphyrins are always increased in clinically manifest PCT, and a total plasma porphyrin determination is most useful for screening. A normal value rules out PCT and other porphyrias that produce blistering skin lesions. If increased, it is useful to determine the plasma fluorescence emission maximum at neutral pH, because a maximum near 619 nm is characteristic of PCT (as well as CEP and HCP) and, most important, excludes VP, which has a distinctly different fluorescence maximum. Increased urinary porphyrins, with a predominance of uroporphyrin and heptacarboxyl porphyrin, is confirmatory. Urine porphyrins are less useful for initial screening because nonspecific increases, especially of coproporphyrin, occur in liver disease and other medical conditions. Urinary ALA may be increased slightly, and PBG is normal. Familial (type 2) can be distinguished from sporadic (type 1) PCT by finding decreased erythrocyte UROD activity (in type 2), or more reliably by finding a disease-related UROD mutation. Type 3 is distinguished from type 1 only by occurrence of PCT in a relative. Biochemical findings in HEP are similar to those in PCT, but with an additional marked increase in erythrocyte zinc protoporphyrin.

**Pseudoporphryia** (also known as pseudo-PCT) presents with skin lesions that closely resemble PCT, but without significant increases in plasma porphyrins. A photosensitizing drug such as a nonsteroidal antiinflammatory agent is sometimes implicated. Both PCT and pseudoporphryia may occur in patients with end-stage renal disease.

**Complications**

Cutaneous blisters may rupture and become infected, sometimes leading to cellulitis. In more-severe disease in patients with end-stage renal disease, repeated infections can be mutilating, as in CEP. Pseudodroscleroderma, with scarring, contraction, and calcification of skin and subcutaneous tissue, is a rare complication. Other complications include advanced liver disease and hepatocellular carcinoma.

**Treatment**

Two specific and effective forms of treatment, namely phlebotomy or low-dose hydroxychloroquine, are available. Susceptibility factors should be removed when possible. The diagnosis of PCT must be firmly established, because conditions that produce identical cutaneous lesions do not respond to these treatments. Treatment can usually be started after demonstrating an increase in plasma total porphyrins and excluding VP by analysis of the fluorescence spectrum at neutral pH, while urine and fecal studies are still pending. Use of alcohol, estrogens (in women), and smoking should be stopped, and patients tested for hepatitis C, HIV, and HFE mutations. Some susceptibility factors and the degree of iron overload as assessed by the serum ferritin concentration, influence the choice of treatment. Phlebotomy is considered standard therapy, and is effective both in children and adults with PCT because it reduces hepatic iron content. Treatment is guided by plasma (or serum) ferritin and porphyrin levels. Hemoglobin or hematocrit levels should be followed to prevent symptomatic anemia. For adults, a unit of blood (≈450 mL) is removed at about 2 wk intervals until a target serum ferritin near the lower limit of normal (≈15 ng/mL) is achieved. A total of 6-8 phlebotomies is often sufficient. After this, plasma porphyrin concentrations continue to fall from pretreatment levels (generally 10-25 µg/dL) to the lower limit of normal (≈1 µg/dL), usually after several more weeks. This is followed by gradual clearing of skin lesions, sometimes including pseudodroscleroderma. Liver function abnormalities may improve, and hepatic siderosis, needle-like inclusions, and red fluorescence of liver tissue will disappear. Although remission usually persists even if ferritin levels later return to normal, it is advisable to follow porphyrin levels and reinstitute phlebotomies if these begin to rise. Infusions of deferoxamine, an iron chelator, may be used when phlebotomy is contraindicated.

An alternative when phlebotomy is contraindicated or poorly tolerated is a low-dose regimen of hydroxychloroquine (or chloroquine). Normal doses of these 4-aminoquinolines antimalarials increase plasma and urinary porphyrin levels and increase photosensitivity in PCT, reflecting an outpouring of porphyrins from the liver. This is accompanied by acute hepatocellular damage, with fever, malaise, nausea, and increased serum transaminases, but is followed by complete remission of the porphyria. These adverse consequences of normal doses are largely avoided by a low-dose regimen (hydroxychloroquine 100 mg or chloroquine 125 mg, of a normal tablet, twice weekly), which can be continued until plasma or urine porphyrins are normalized. There is at least some risk of retinopathy, which may be lower with hydroxychloroquine. The mechanism of action of 4-aminoquinolines in PCT is not known but is quite specific, because these drugs are not useful in other porphyrias. Recent studies indicate that low-dose hydroxychloroquine is as safe and effective as phlebotomy in PCT.

In patients with PCT and hepatitis C, PCT should be treated first because this condition is more symptomatic and can be treated more quickly and effectively. Treatment of PCT by phlebotomy may not be possible once interferon-rabirivirin treatment is complicated by anemia. Moreover, treatment of hepatitis C may be more effective after iron reduction.

PCT in patients with end-stage renal disease is often more severe and difficult to treat. However, erythropoietin administration can correct anemia, mobilize iron, and support phlebotomy in many cases. Improvement after renal transplantation may be partly from resumption of endogenous erythropoietic production. Liver imaging and a serum α-fetoprotein determination may be advisable in all PCT patients, perhaps at 6-12 mo intervals, for early detection of hepatocellular carcinoma. Finding low-erythrocyte UROD activity or a UROD mutation identifies those with an underlying genetic predisposition, which does not alter treatment but is useful for genetic counseling.

**Prognosis**

PCT is the most readily treated form of porphyria, and complete remission is expected with treatment either by phlebotomy or low-dose hydroxychloroquine. There is little information on rates of recurrence and long-term outlook. Risk for hepatocellular carcinoma is increased, and some susceptibility factors such as hepatitis C can lead to complications even after PCT is in remission.

**Prevention and Genetic Counseling**

Patients with PCT may have concerns about risk to other family members. A heritable UROD mutation can usually be detected or excluded by measuring erythrocyte UROD activity, although DNA studies are more sensitive. Relatives of patients with UROD mutations have an increased risk for developing PCT, and may have increased motivation to avoid adverse behaviors such as ethanol and tobacco use and exposures to hepatitis C and HIV. Such counseling would be given to anyone, however. The finding of HFE mutations, and especially C282Y, should prompt screening of relatives, some of whom may be C282Y homozygotes and warrant lifelong monitoring of serum ferritin.
a pattern consistent with severe UROD deficiency. This rare disorder has no particular racial predominance.

**Etiology**

HEP is an autosomal recessive disorder, although most patients have inherited a different mutation from unrelated parents. In contrast to most mutations in familial (type 2) PCT, most causing HEP are associated with expression of some residual enzyme activity. At least 1 genotype is associated with the predominant excretion of pentacarbboxyl porphyrin.

**Pathology and Pathogenesis**

Excess porphyrins originate primarily from the liver in HEP, although the substantial increase in erythrocyte zinc protoporphyrin indicates that the heme biosynthetic pathway is also impaired in bone marrow erythroid cells. Apparently, porphyrinogens accumulate in the marrow while hemoglobin synthesis is most active, and are metabolized to protoporphyrin after hemoglobin synthesis is complete. The cutaneous lesions are a result of photoactivation of porphyrins in skin, as in other cutaneous porphyrias.

**Clinical Manifestations**

Like CEP, this disease usually presents with blistering skin lesions, hypertrichosis, scarring, and red urine in infancy or childhood. Sclerodermoid skin changes are sometimes prominent. Unusually mild cases have been described. Concurrent conditions that affect liver function can alter disease severity. For example, the disease became manifest because of hepatitis A in a 2 yr old child, and then improved with recovery of liver function.

**Laboratory Findings**

Biochemical findings resemble those in PCT with accumulation and excretion of uroporphyrin, heptacarboxyl porphyrin, and isocoproporphyrin. But in addition, erythrocyte zinc protoporphyrin is substantially increased.

**Diagnosis and Differential Diagnosis**

HEP is distinguished from CEP by increases in both uroporphyrin and heptacarboxyl porphyrin, and isocoproporphyrins. In CEP, the excess erythrocyte porphyrins are predominantly uroporphyrin and coproporphyrin rather than protoporphyrin. Blistering skin lesions are unusual in EPP, the excess erythrocyte protoporphyrin in that disease is free and not complexed with zinc, and urinary porphyrins are normal.

**Treatment and Prognosis**

Avoiding sunlight exposure is most important in managing this disease, as in CEP. Oral charcoal was helpful in a severe case associated with dyserthropoiesis. Phlebotomy has shown little or no benefit. The outlook depends on the severity of the enzyme deficiency and may be favorable if sunlight can be avoided.

**Prevention and Genetic Counseling**

As part of genetic counseling in affected families, it is feasible to diagnose HEP in utero, either by analysis of porphyrins in amniotic fluid or DNA studies.

**HEREDITARY COPROPORPHYRIA**

This autosomal dominant hepatic porphyria is caused by a deficiency of CPOX. The disease presents with acute attacks, as in AIP. Cutaneous photosensitivity may occur, but much less commonly than in VP. Rare homozygous cases present in childhood.

**Etiology**

A partial (50%) deficiency in CPOX activity has been found in all cells studied from patients with HCP. A much more profound deficiency is found in homozygous cases. Human CPOX is a homodimer composed of 39 kDa subunits, and contains no metals or prosthetic groups. The enzyme requires molecular oxygen, and is localized in the mitochondrial intermembrane space. A single active site on the enzyme catalyzes the oxidative decarboxylation of 2 of the 4 propionic acid groups of coproporphyrinogen III to form the 2 vinyl groups at positions 2 and 4, on rings A and B, respectively, of protoporphyrin IX (see Fig. 91-1). Most of the intermediate tricarboxyl porphyrinogen, termed harderoporphyrinogen, is not released before undergoing the second decarboxylation to protoporphyrinogen IX. Coproporphyrinogen I is not a substrate for this enzyme.

The human CPOX gene contains 7 exons and is located on chromosome 3q12.1. A single promoter contains elements for both housekeeping and erythroid-specific expression. A variety of CPOX gene mutations have been described in HCP, with a predominance of nonsense mutations and no genotype-phenotype correlations. Harderoporphyrin, an autosomal recessive biochemical variant form of HCP, is caused by CPOX mutations that impair substrate binding, leading to premature release of harderoporphyrinogen.

**Epidemiology**

HEP is less common than AIP and VP, but its prevalence has not been carefully estimated. There is no obvious racial predominance. Homozygous HCP is rare and presents during childhood. Harderoporphyrin, a biochemically distinguishable variant of HCP, has been recognized in heteroallelic and homoallelic forms.

**Pathology and Pathogenesis**

Increased ALA and PBG during acute attacks of HCP may be explained by induction of ALAS1 and by the normally relatively low activity of PBGD in the liver. Hepatic ALAS1 is increased during acute attacks, but is normal when the disease is latent and porphyrin precursor excretion is normal. Because coproporphyrinogen III concentration in the liver is probably less than the Km for CPOX, the reaction rate is likely to be determined in part by substrate concentration. The substrate coproporphyrinogen appears to be lost more readily from the liver cell than, for example, uroporphyrinogen, especially when heme synthesis is stimulated. Coproporphyrin and coproporphyrinogen are both transported into bile and excreted in urine, and do not appear to accumulate in the liver in HCP.

**Clinical Manifestations**

Symptoms are identical to those of AIP except that attacks are generally milder, and cutaneous lesions that resemble those in PCT develop occasionally. Severe motor neuropathy and respiratory paralysis can occur. Like other acute porphyrias, HCP is almost always latent before puberty, and symptoms are most common in adult women. Attacks are precipitated by the same factors that cause attacks in AIP, including fasting, oral contraceptive steroids, and hormone increases during the luteal phase of the menstrual cycle. Concomitant liver diseases may increase porphyrin retention and photosensitivity. The risk of hepatocellular carcinoma is increased, as in other acute porphyrias.

The clinical features of homozygous HCP or harderoporphyria, which begin in early childhood, may include jaundice, hemolytic anemia, hepatosplenomegaly, and skin photosensitivity. These symptoms are generally quite distinct from those seen in heterozygotes.

**Laboratory Findings**

The porphyrin precursors ALA and PBG are increased during acute attacks, but may decrease more rapidly than in AIP. Marked increases in coproporphyrin III in urine and feces are more persistent. In homozygous HCP, porphyrin excretion may be more markedly increased and is accompanied by substantial increases in erythrocyte zinc protoporphyrin. Harderoporphyrin is characterized by a marked increase in fecal excretion of harderoporphyrin (tricarboxyl porphyrin) as well as coproporphyrin. Plasma porphyrins are usually normal or only slightly increased.

**Diagnosis and Differential Diagnosis**

The diagnosis of HCP is readily established in patients with clinically manifest disease, although urinary ALA, PBG, and uroporphyrin may revert to normal more quickly than in AIP. Urinary coproporphyrin
III is increased. Urinary porphyrins, especially coproporphyrin, can be increased in many medical conditions such as liver disease, and small increases may not be clinically significant and lead to an incorrect diagnosis of HCP. Fecal porphyrins are mostly coproporphyrin (isomer III) in HCP, whereas in VP, coproporphyrin III and protoporphyrin are often increased approximately equally. Plasma porphyrins are usually normal in HCP and increased in VP.

The ratio of fecal coproporphyrin III to coproporphyrin I is especially sensitive for detecting latent heterozygotes (especially adults). Assays for CPOX, a mitochondrial enzyme, require cells such as lymphocytes and are not widely available. Identification of a CPOX mutation in an index case greatly facilitates screening family members.

**Treatment and Prognosis**

Acute attacks of HCP are treated as in AIP, which includes intravenous hemin and identifying and avoiding precipitating factors. Cholestyramine may be of some value for photosensitivity occurring with liver dysfunction. Phlebotomy and chloroquine are not effective. Gonadotropin-releasing hormone analogs can be effective for prevention of cyclic attacks. The prognosis is generally better than in AIP.

**Prevention and Genetic Counseling**

These are the same as in other acute porphyrinas.

**Variegate Porphyria**

This hepatic porphyria is caused by a deficiency of protoporphyrinogen oxidase (PPOX), which is inherited as an autosomal dominant trait. The disorder is termed variegate because it can present with neurologic or cutaneous manifestations. Other terms have included porphyria variegate, protocoproporphyria, and South African genetic porphyria. Rare cases of homozygous VP are symptomatic in childhood.

**Etiology**

PPOX is approximately half normal in all cells studied in patients with VP. The enzyme is more markedly deficient in rare cases of homozygous VP, with approximately half-normal enzyme activity in parents.

Human PPOX is a homodimer that contains flavin adenine dinucleotide and is localized to the cytosolic side of the inner mitochondrial membrane. Membrane-binding domains may be docked onto human FECH, the next enzyme in the pathway, which is embedded in the opposite side of the membrane. PPOX catalyzes the oxidation of protoporphyrinogen IX to protoporphyrin IX by the removal of 6 hydrogen atoms (see Fig. 91-1). The enzyme requires molecular oxygen. The substrate is readily oxidized nonenzymatically to protoporphyrin under aerobic conditions, or if exported into the cytosol. PPOX is highly specific for protoporphyrinogen IX, and is inhibited by tetrapyrroles such as heme, biliverdin, and bilirubin and by certain herbicides that cause protoporphyrin to accumulate and induce photosensitivity in plants. Inhibition by bilirubin may account for decreased PPOX activity in Gilbert disease.

The human PPOX gene on chromosome 1q22-q23 consists of 1 noncoding and 12 coding exons. A single PPOX transcript is produced in a variety of tissues, but putative transcriptional element binding sequences may allow for erythroid-specific expression. Many PPOX mutations have been reported in VP families. A missense mutation, R59W, is prevalent in South Africa. No convincing genotype-phenotype correlations have been identified. Mutations in homozygous cases of VP are more likely to encode enzyme proteins with residual activity.

**Epidemiology**

VP is less common than AIP in most countries. The R59W mutation is highly prevalent in South African whites (3 in 1,000 in this population). This example of genetic drift or “founder effect” has been traced to a man or his wife who emigrated from Holland to South Africa in 1688. In Finland, the prevalence is 1.3 in 100,000 people and is about as common as AIP.

**Pathology and Pathogenesis**

Acute attacks develop in a minority (approximately 25%) of heterozygotes for PPOX deficiency, and are often attributable to drugs, steroids, and nutritional factors that play a role in other acute porphyrinas. Protoporphyrinogen IX accumulates and undergoes autoxidation to protoporphyrin IX. Coproporphyrinogen III may accumulate as the result of a close functional association between PPOX in the inner mitochondrial membrane and CPOX in the intermembrane space. Liver porphyrin content is not increased. The increased porphyrin content in plasma consists of porphyrin-peptide conjugates, which may be formed from protoporphyrinogen. Increased ALA and PBG during acute attacks may be explained, as in HCP, by induction of ALAS1 by exacerbating factors, and by the normally relatively low activity of PBGD in liver. Furthermore, PBGD is inhibited by protoporphyrinogen, the substrate for PPOX.

**Clinical Manifestations**

Symptoms develop in some heterozygotes after puberty. Neurovisceral symptoms occurring as acute attacks are identical to AIP but are generally milder and less often fatal. Drugs, steroids, and nutritional alterations such as fasting, which are harmful in AIP, can also induce attacks of VP. Attacks occur equally in males and females, at least in South Africa. Cutaneous fragility, vesicles, bullae, hyperpigmentation, and hypertrichosis of sun-exposed areas are much more common than in HCP. They are likely to occur apart from and be more long lasting than the neurovisceral symptoms. Oral contraceptives can precipitate cutaneous manifestations. Acute attacks have become less common, and skin manifestations are more frequently the initial presentation; this may be due to earlier diagnosis and counseling. The risk of hepatocellular carcinoma is increased.

Symptoms of homozygous VP begin in infancy or childhood. These children generally have severe photosensitivity, neurologic symptoms, convulsions, developmental disturbances, and sometimes growth retardation, but do not have acute attacks.

**Laboratory Findings**

Urinary ALA, PBG, and uroporphyrin are increased during acute attacks but often less so than in AIP, and may be normal or only slightly increased during remission. Plasma porphyrins, urinary coproporphyrin III, and fecal coproporphyrin III and protoporphyrin are more persistently increased between attacks. Erythrocyte zinc protoporphyrin levels are markedly increased in homozygous VP and may be modestly increased in heterozygous cases.

**Diagnosis and Differential Diagnosis**

VP is readily distinguished from AIP and HCP, which also present with acute attacks and increases in PBG. Plasma porphyrin analysis is especially useful, because the plasma porphyrins in VP are tightly protein bound, resulting in a characteristic fluorescence emission spectrum at neutral pH. Fecal porphyrins are increased, with approximately equal amounts of coproporphyrin III and protoporphyrin. Fluorometric detection of plasma porphyrins is more sensitive than stool porphyrin analysis in asymptomatic VP. PPOX assays using cells that contain mitochondria, such as lymphocytes, are sensitive for identifying asymptomatic carriers but are not widely available. Knowing the PPOX mutation in an index case enables the identification of relatives who carry the same mutation.

**Treatment**

Acute attacks are treated as in AIP. Hemin is beneficial for acute attacks but not for cutaneous symptoms. Light protection is important in patients with skin manifestations, using long-sleeved clothing, gloves, a broad-brimmed hat, and opaque sunscreen preparations. Exposure to short-wavelength UV light, which does not excite porphyrins, may increase skin pigmentation and provide some protection. Phlebotomy and chloroquine are not effective. Surprisingly, oral activated charcoal was reported to increase porphyrin levels and worsen skin manifestations.
Prognosis and Prevention
The outlook of patients with VP has improved, which may be attributed to improved treatment, earlier diagnosis, and detection of latent cases. Cyclic acute attacks in women can be prevented with a gonadotropin-releasing hormone analog, as in AIP. A diagnosis of VP or any other acute porphyria should not lead to difficulty obtaining insurance, because the prognosis is usually good once the diagnosis is established.

Genetic Counseling
This is the same as in other acute porphyrinas.

ERYTHROPOIETIC PROTOPORPHYRIA
In this autosomal recessive disorder, protoporphyrin accumulates as the result of a marked deficiency of FECH, the last enzyme in the heme biosynthetic pathway, because of FECH mutations. EPP is sometimes termed protoporphyrinia or erythrohepatic protoporphyrinia, although the liver does not contribute substantially to production of excess protoporphyrin in uncomplicated cases. XLP is a genetically distinct form of porphyria that is less common than EPP but with the same phenotype, and is a result of gain of function ALAS2 mutations.

Etiology
FECH, the enzyme that is deficient in EPP, catalyzes the final step in heme synthesis, which is insertion of ferrous iron ($Fe^{2+}$) into protoporphyrin IX (see Fig. 91-1). The enzyme is also termed heme synthetase or protoporphyrin ferrolyase. The human enzyme is a dimer, and each homodimer contains a [2Fe-2S] cluster, which may have a role in bridging homodimers. FECH is found in the mitochondrial inner membrane where its active site faces the mitochondrial matrix. It may be associated with complex I of the mitochondrial electron transport chain, and the ferrous iron substrate may be produced upon nicotinamide adenine dinucleotide oxidation. FECH is specific for the reduced form of iron, but can utilize other metals such as Zn$^{2+}$ and Co$^{2+}$ and other dicarboxyl porphyrins. Accumulation of free protoporphyrin rather than zinc protoporphyrin in EPP indicates that formation of the latter is dependent on FECH activity in vivo.

The human FECH gene is located on chromosome 18q21.3, has a single promoter sequence, and contains 11 exons. Two mRNAs of 1.6 and 2.5 kb were described, which may be explained by the use of 2 alternative polyadenylation signals. The larger transcript is more abundant in murine erythroid cells, suggesting erythroid-specific regulation of FECH. A variety of FECH mutations have been reported in EPP, including missense, nonsense, and splicing mutations, small and large deletions, and an insertion.

The inheritance of 2 alleles associated with reduced FECH activity is required for disease expression. This is consistent with FECH activities as low as 15-25% of normal in EPP patients. In most patients, a disabling mutation on 1 FECH allele is combined with a common variant affecting the other allele. This common variant FECH allele (IVS3-48T > C) produces less-than-normal amounts of enzyme because it expresses an aberrantly spliced mRNA that is degraded by a nonsense-mediated RNA decay mechanism. The IVS3-48T > C FECH variant by itself does not cause disease, even when homozygous. In a few families, 2 severe FECH mutations have been found, without the IVS3-48T > C allele. EPP with autosomal recessive inheritance occurs naturally in cattle and in mouse models.

XLP is associated with gain-of-function deletions in the last exon of ALAS2. These lesions delete the last 10-20 amino acids of the ALAS2 polypeptide and apparently make the enzyme more stable. Free protoporphyrin predominates in erythrocytes in these cases, but because FECH activity is normal the proportion of zinc protoporphyrin is greater than in classic EPP. XLP accounts for approximately 2% of cases with the EPP phenotype in Europe and approximately 10% of cases in North America.

EPP is sometimes associated with myelodysplastic syndromes and expansion of a clone of hematopoietic cells with deletion of one FECH allele or other FECH mutations. In such cases, there is late onset of the disease.

Epidemiology
EPP is the most common porphyria to cause symptoms in children, but is often not diagnosed until adult life. Overall it is the third most common porphyria, although its prevalence is not precisely known (see Table 91-2). It is described mostly in white people, but occurs in other races. The IVS3-48T > C splice variant is common in whites and East Asians, but rare in Africans, which explains lower disease prevalence in populations of African origin.

Pathology and Pathogenesis
FECH is deficient in all tissues in EPP, but bone marrow reticuloctyes are thought to be the primary source of the excess protoporphyrin, some of which enters plasma and circulates to the skin. Circulating erythrocytes are no longer synthesizing heme and hemoglobin, but they contain excess free protoporphyrin, which also contributes. In XLP caused by terminal deletions in exon 11 of ALAS2, all intermediates of the heme pathway are overproduced and ultimately accumulate in bone marrow erythroblasts as protoporphyrin. FECH is not deficient in the variant form, and this enzyme chelates some of the excess protoporphyrin with zinc. An aberrantly spliced mitoferrin transcript, which limits iron transport into mitochondria, has also been described in this condition. The liver functions as an excretory organ rather than a major source for excess protoporphyrin. But FECH deficiency in the skin and liver may be important, as tissue transplantation studies in mice suggest that skin photosensitivity and liver damage occur only when FECH is deficient in these tissues.

Patients with EPP and XLP are maximally sensitive to light in the 400 nm range, which corresponds to the so-called Soret band (the narrow peak absorption maximum that is characteristic for protoporphyrin and other porphyrins). Having absorbed light, porphyrins enter an excited energy state and release energy as fluorescence, singlet oxygen, and other reactive oxygen species. Tissue damage is accompanied by lipid peroxidation, oxidation of amino acids, crosslinking of proteins in cell membranes, and damage to capillary endothelial cells. Such damage may be mediated by photoactivation of the complement system and release of histamine, kinins, and chemotactic factors. Repeated acute damage leads to thickening of the vessel walls and perivascular deposits from accumulation of serum components. Deposition of amorphous material containing immunoglobulin, complement components, glycoproteins, acid glycosaminoglycans, and lipids around blood vessels occurs in the upper dermis.

There is little evidence for impaired erythropoiesis or hemolysis in EPP. However, mild anemia with microcytosis, hypochromia and reticulocytosis is common. Iron accumulation in erythroblasts and ring sideroblasts have been noted in bone marrow in some patients. Decreased transferrin saturation and low or low-normal serum ferritin suggest iron deficiency. Iron status should be carefully evaluated in EPP patients, keeping in mind that iron deficiency may lead to further increases in protoporphyrin and increase the risk for cholestasis. Oral iron supplements are often poorly absorbed in EPP, which is explained. Some patients report increased photosensitivity when given iron supplements, but whether this is from transient increases in porphyrins when iron deficiency is corrected and erythropoiesis increases is not known.

Liver damage that develops in a small proportion of EPP and XLP patients is attributed to excess protoporphyrin, which is cholestatic, insoluble in water and excreted only by hepatic uptake and biliary excretion. Some may be reabsorbed by the intestine and undergo enterohepatic circulation. With cholestasis the excess protoporphyrin that accumulates in the liver can form crystalline structures in hepatic and perivascular deposits, and impair mitochondrial function.

Clinical Manifestations
Symptoms of cutaneous photosensitivity begin in childhood, and consist of pain, redness, and itching occurring within minutes of sunlight exposure. Swelling may resemble angioneurotic edema, and solar urticaria. Symptoms are usually worse in the spring and summer. Petechiae and purpuric lesions may be seen, but blisters are usually absent. Chronic changes may include lichenification, leathery pseudoacne,
labial grooving, and nail changes, but changes in pigmentation and pronounced scarring are unusual. Although physical findings in EPP and XLP may not be impressive, the symptoms significantly impair quality of life to a greater extent in PCT and VP. An association between autosomal recessive EPP and seasonal palmar keratoderma is unexplained. Neuropathy develops only in some patients with severe hepatic decompensation.

Unless hepatic or other complications develop, protoporphyrin levels and symptoms of photosensitivity remain remarkably stable for many years in most patients. Factors that exacerbate hepatic protoporphyrin levels play little or no role in EPP or XLP. Mild, unexplained hypertriglyceridemia has been described. Erythrocyte protoporphyrin levels may decrease and sunlight tolerance may improve during pregnancy, which is unexplained.

**Laboratory Findings**
Protoporphyrin is substantially increased in circulating erythrocytes in EPP, and consists almost entirely of free protoporphyrin. In a variant form of EPP caused by ALAS2 exon 11 deletions, both zinc protoporphyrin and free protoporphyrin are increased, although the latter still predominates. Protoporphyrin is also increased in bone marrow, plasma, bile, and feces. Other porphyrins and porphyrin precursors are normal in uncomplicated EPP.

**Diagnosis and Differential Diagnosis**
A diagnosis of EPP is confirmed primarily by finding a substantially elevated concentration of erythrocyte protoporphyrin, which is predominantly metal-free and not complexed with zinc. In XLP, both free and zinc complexed protoporphyrins are elevated. Erythrocyte total protoporphyrin levels are on average higher in XLP more variable in EPP, possible reflecting differences in severity of the many reported FECH mutations. Erythrocyte zinc protoporphyrin concentration is increased in some homozygous porphyrias, iron deficiency, lead poisoning, anemia of chronic disease, hemolytic conditions, and many other erythrocytic disorders. Many assays for erythrocyte protoporphyrin or “free erythrocyte protoporphyrin” measure only zinc protoporphyrin (i.e., iron-free rather than metal-free protoporphyrin). Therefore, reports must be interpreted with care, and confirmation obtained from a laboratory that reliably fractionates metal-free and zinc protoporphyrin.

Plasma total porphyrin concentration is often less increased in EPP than in other cutaneous porphyrias, and may be normal. Great care must be taken to avoid light exposure during sample processing, because plasma porphyrins in EPP are particularly subject to photodegradation. Urinary porphyrin precursors and porphyrins are not increased. Measurement of FECH activity requires cells containing mitochondria and is not widely available. A greater than expected proportion of zinc protoporphyrin (more than ~15% of the total) in erythrocytes is important in identifying XLP. DNA studies are increasingly important for confirming FECH or ALAS2 mutations and for genetic counseling.

Life-threatening protoporphyric hepatopathy is heralded by increasingly abnormal liver function tests, increasing erythrocyte and plasma protoporphyrin levels, and worsening photosensitivity. Increases in urinary porphyrins, especially coproporphyrin, in this setting are attributable to liver dysfunction.

**Complications**
Biliary stones containing protoporphyrin are sometimes symptomatic and require cholecystectomy. Protoporphyrin hepatopathy occurs in less than 5% of EPP patients, including children, and may be chronic or progress rapidly to death from liver failure. This liver disease is sometimes the major presenting feature of EPP. In XLP, liver disease may be more frequent and in 1 report of 8 families, 17% of patients had overt liver dysfunction. Protoporphyrin hepatopathy can cause acute upper abdominal pain suggesting biliary obstruction, and unnecessary laparotomy to exclude this possibility can be detrimental. Concurrent conditions that impair liver function, such as viral hepatitis, alcohol intake, iron deficiency, fasting, or oral contraceptive steroids, may contribute. Liver histology shows marked deposition of protoporphyrin in liver cells and bile canaliculi. Patients with protoporphyric liver failure most often have FECH “null mutations” and the IVS3-48T>C hypoexpression allele, but some may have 2 severe mutant FECH alleles or XLP caused by ALAS2 exon 11 deletions. The bone marrow is probably the major source of protoporphyrin, even in EPP patients with hepatic failure.

**Treatment**
Exposure to sunlight should be avoided, which is aided by wearing closely woven clothing. Oral beta-carotene leads to clinical improvement and greater tolerance to light in some patients, usually 1–3 mo after starting treatment. In most adults, doses of 120-180 mg daily will maintain serum carotene levels in the recommended range of 600-800 mg/dL, but doses up to 300 mg daily may be needed. Mild skin discoloration from carotenemia is expected. The recommended product is Lumnite, which was initially developed as a drug for treating this disease, rather than nutritional products that are less standardized. Beta-carotene may quench singlet oxygen or free radicals, but does not substantially alter circulating porphyrin levels. Better tolerance of sunlight may result in tanning, which provides additional protection. Oral cysteine may also quench excited oxygen species and was found to increase tolerance to sunlight in EPP.

Measures to darken the skin may also be helpful. This may be accomplished by narrow-band UV-B phototherapy or with topical products such as dihydroxyacetone and lawsome (naphthaquinone). Afamelanotide, a synthetic analog of melanocyte-stimulating hormone shows promise for increasing sunlight tolerance in EPP and XLP and is currently in Phase 3 trials in the United States. Caloric restriction and drugs or hormone preparations that impair hepatic excretory function should be avoided, and iron deficiency should be corrected if present. Vitamin D supplementation and hepatitides A and B vaccination are recommended.

Treatment of protoporphyric hepatopathy must be individualized and results are unpredictable. Ursodeoxycholic acid may be of some value in early stages. Cholestyramine or activated charcoal may interrupt the enterohepatic circulation of protoporphyrin, promote its fecal excretion, and reduce liver protoporphyrin content. Spontaneous resolution may occur, especially if another reversible cause of liver dysfunction, such as viral hepatitis or alcohol abuse, is contributing. In patients with severe hepatic decompensation, combined treatment with plasmapheresis, transfusion to suppress erythropoiesis, intravenous hemin to suppress erythroid and hepatic protoporphyrin production, ursodeoxycholic acid, vitamin E, and cholestryamine may be beneficial.

Motor neuropathy resembling that seen in acute porphyrias sometimes develops in EPP patients with liver disease before or after transplantation and is sometimes reversible. Artificial lights, such as operating room lights during liver transplantation or other surgery, may cause severe photosensitivity, with extensive burns of the skin and peritoneum and photodamage of circulating erythrocytes. With continued progression of liver disease, liver transplantation may be considered. Although liver disease may recur in the transplanted liver as a result of continued bone marrow production of excess protoporphyrin, outcomes are comparable to transplantation for other types of liver disease. Bone marrow transplantation should also be considered after liver transplantation if a suitable donor is available.

**Prognosis**
Typical EPP patients have lifelong photosensitivity but can otherwise expect normal longevity. Protoporphyrin liver disease is often life-threatening; however, the incidence is low.

**Prevention**
Symptoms can be prevented by avoiding sunlight. Avoiding agents that may cause liver damage may help prevent liver complications.
Genetic Counseling
DNA studies to identify \textit{FECH} mutations, the common IVS3–48T>C \textit{FECH} hypoexpression allele, or ALAS2 exon 11 deletions are increasingly important for genetic counseling. EPP may improve during pregnancy. In classic EPP, DNA studies in both parents can predict the risk for EPP occurring in an offspring.

Dual Porphyria
\textit{Dual porphyria} refers to patients with porphyria who have deficiencies of more than 1 enzyme of the heme biosynthetic pathway. An unusual pattern of porphyrin precursors and porphyrins may suggest the presence of 2 enzyme deficiencies. Mutations of 2 heme pathway enzymes have been documented in only 2 patients with porphyria. One presented with acute porphyria and had heterozygous mutations in both the \textit{CPOX} and \textit{ALAD} genes. The other had symptoms of AIP and PCT and was documented to have both \textit{PBGD} and \textit{UROD} mutations. In other reported cases, 1 or both enzyme deficiencies were based on enzyme measurements.

Porphyria Resulting from Tumors
Very rarely, hepatocellular tumors contain and presumably produce excess porphyrins, but such cases have not been studied carefully. Hepatocellular carcinomas complicating PCT and acute hepatic porphyrias usually are not described as containing large amounts of porphyrins. Erythropoietic porphyrias can develop late in life from clonal expansion of erythroid cells containing a specific enzyme deficiency in patients who have developed myelodysplastic or myeloproliferative syndromes.

\textit{Bibliography is available at Expert Consult.}
Bibliography

General

Acute Porphyrias

Congenital Erythropoietic Porphyria

Porphyria Cutanea Tarda

Erythropoietic Protoporphyria
Glucose has a central role in fuel economy and is a source of energy storage in the form of glycogen, fat, and protein (see Chapter 87). As an immediate source of energy, glucose provides 38 mol of adenosine triphosphate (ATP) per mole of glucose oxidized. Glucose is essential for energy metabolism in the brain where it is usually the preferred substrate and where its utilization accounts for nearly all of the brain's oxygen consumption. Cerebral glucose uptake occurs through a glucose transporter molecule or molecules that are not regulated by insulin. Cerebral transport of glucose is a GLUT1, carrier-mediated, facilitated diffusion process that is dependent on blood glucose concentration. Hence, low concentrations of blood glucose result in cerebral glucopenia. Deficiency of brain glucose transporters can result in seizures because of low cerebral and cerebrospinal fluid (CSF) glucose concentrations (hypoglycemia) despite normal blood glucose levels. To maintain the blood glucose concentration and prevent it from falling precipitously to levels that impair brain function, an elaborate regulatory system has evolved.

The defense against hypoglycemia is integrated by the autonomic nervous system and by hormones that act in concert to enhance glucose production through enzymatic modulation of glycolysis and gluconeogenesis, while simultaneously limiting peripheral glucose utilization which conserves glucose for cerebral metabolism. Hypoglycemia represents a defect in one or several of the complex interactions that normally integrate glucose homeostasis during feeding and fasting. This process is particularly important for neonates, in whom there is an abrupt transition from intrauterine life, characterized by dependence on transplacental glucose supply, to extrauterine life, characterized ultimately by the autonomous ability to maintain euglycemia. Because prematurity or placental insufficiency may limit tissue nutrient deposits, and genetic abnormalities in enzymes or hormones may become evident in the neonate, hypoglycemia is common in the neonatal period.

**DEFINITION**

In neonates, there is not always an obvious correlation between blood glucose concentration and the classic clinical manifestations of hypoglycemia. The absence of symptoms does not indicate that glucose concentration is normal and has not fallen to less than some optimal level for maintaining brain metabolism. There is evidence that hypoglycemia and ischemia may potentiate the role of hypoglycemia in causing permanent brain damage. Consequently, the lower limit of accepted normality of the blood glucose level in newborn infants with associated illness that already impairs cerebral metabolism has not been determined (see Chapter 107). Out of concern for possible neurologic, intellectual, or psychologic sequelae in later life, most authorities recommend that any value of blood glucose <55 mg/dL in neonates be viewed with suspicion and vigorously treated. This is particularly applicable after the initial 2-3 hr of life, when glucose normally has reached its nadir; subsequently, blood glucose levels begin to rise and achieve values of 50 mg/dL or higher after 12-24 hr. By day 3 of life in normal full-term newborns, blood glucose averages approximately 60 mg/dL. In older infants and children, a whole blood glucose concentration of <55 mg/dL (10-15% higher for serum or plasma) represents hypoglycemia, because counterregulatory mechanisms are activated at these glucose concentrations.

**SIGNIFICANCE AND SEQUELAE**

Most of the endogenous hepatic glucose production in infants and young children, which occurs several hours after feeding and during fasting, can be accounted for by brain metabolism. Because the brain grows most rapidly in the 1st yr of life and because the larger proportion of glucose turnover is used for brain metabolism, sustained or repetitive hypoglycemia in infants and children can retard brain development and function. Transient isolated and asymptomatic hypoglycemia of short duration does not appear to be associated with these severe sequelae. In the rapidly growing brain, glucose may also be a source of membrane lipids and, together with protein synthesis it can provide structural proteins and myelination that are important for normal brain maturation. Under conditions of severe and sustained hypoglycemia, these cerebral structural substrates may become degraded to energy-usable intermediates such as lactate, pyruvate, amino acids, and ketocids, which can support brain metabolism at the expense of brain growth. The capacity of the newborn brain to take up and oxidize ketone bodies is about 5-fold greater than that of the adult brain. However, the capacity of the liver to produce ketone bodies is limited in the immediate newborn period, especially in the presence of hyperinsulinism, which acutely inhibits hepatic glucose output, lipolysis, and ketogenesis, thereby depriving the brain of any alternate fuel sources. Although the brain may metabolize ketones, these alternate fuels cannot completely replace glucose as an essential central nervous system (CNS) fuel. The deprivation of the brain's major energy source during hypoglycemia and the limited availability of alternate fuel sources during hyperinsulinism have predictable adverse consequences on brain metabolism and growth: decreased brain oxygen consumption and increased breakdown of endogenous structural components with destruction of functional membrane integrity.

The major long-term sequelae of severe, prolonged hypoglycemia are cognitive impairment, recurrent seizure activity, cerebral palsy and autonomic dysregulation. Subtle effects on personality are also possible but have not been clearly defined. Permanent neurologic sequelae are present in 25-50% of patients with severe recurrent symptomatic hypoglycemia who are younger than 6 mo of age. These sequelae may be reflected in pathologic changes characterized by reduced myelination in cerebral white matter and atrophy of the cerebral cortex, reflected in enlargement of the sulci and thinning of the gyri of the brain. These sequelae also are more likely when alternative fuel sources are limited,
as occurs with hyperinsulinism, when the episodes of hypoglycemia are repetitive or prolonged, or when they are compounded by hypoxia. There is no precise knowledge relating the duration or severity of hypoglycemia to subsequent neurologic development of children in a predictable manner. Although less common, hypoglycemia in older children may also produce long-term neurologic defects through neonatal death mediated, in part, by cerebral excitotoxins released during hypoglycemia.

**SUBSTRATE, ENZYME, AND HORMONAL INTEGRATION OF GLUCOSE HOMEOSTASIS**

**In the Newborn**

See Chapter 107.

Under nonstressed conditions, fetal glucose is derived entirely from the mother through placental transfer. Therefore, fetal glucose concentration usually reflects, but is slightly lower than, maternal glucose levels. Catecholamine release, which occurs with fetal stress such as hypoxia, mobilizes fetal glucose and free fatty acids (FFAs) through β-adrenergic mechanisms, reflecting β-adrenergic activity in fetal liver and adipose tissue. Catecholamines may also inhibit fetal insulin and stimulate glucagon release.

The acute interruption of maternal glucose transfer to the fetus at delivery imposes an immediate need to mobilize endogenous glucose. Three related events facilitate this transition: changes in hormones, changes in their receptors, and changes in key enzyme activity. There is a 3–5-fold abrupt increase in glucagon concentration within minutes to hours of birth. The level of insulin usually falls initially and remains in the basal range for several days without demonstrating the usual brisk response to physiologic stimuli such as glucose. A dramatic surge in spontaneous catecholamine secretion is also characteristic. Epinephrine can also augment growth hormone secretion by α-adrenergic mechanisms; growth hormone levels are elevated at birth. Acting in concert, these hormonal changes at birth mobilize glucose via glycolysis and gluconeogenesis, activate lipolysis, and promote ketogenesis. As a result of these processes, plasma glucose concentration stabilizes after a transient decrease immediately after birth, liver glycogen stores become rapidly depleted within hours of birth, and gluconeogenesis from alanine, a major gluconeogenic amino acid, can account for approximately 10% of glucose turnover in the human newborn infant by several hours of age. FFA concentrations also increase sharply in concert with the surges in glucagon and epinephrine, and are followed later by rises in ketone bodies. Glucose is thus partially spared for brain utilization while FFAs and ketones provide alternative fuel sources for muscle as well as essential gluconeogenic factors such as acetyl coenzyme A (CoA) and the reduced form of nicotinamide adenine dinucleotide from hepatic fatty acid oxidation, which is required to drive gluconeogenesis.

In the early postnatal period, responses of the endocrine pancreas favor glucagon secretion so that blood glucose concentration can be maintained. These adaptive changes in hormone secretion are paralleled by similarly striking adaptive changes in hormone receptors. Key enzymes involved in glucose production also change dramatically in the perinatal period. Thus, there is a rapid fall in glycolgen synthase activity and a sharp rise in phosphorylase activity after delivery. Similarly, the amount of the rate-limiting enzyme for gluconeogenesis, phosphoenolpyruvate carboxykinase, rises dramatically after birth, activated in part by the surge in glucagon and the fall in insulin. This framework can explain several causes of neonatal hypoglycemia based on inappropriate changes in hormone secretion and unavailability of adequate reserves of substrates in the form of hepatic glycogen, muscle as a source of amino acids for gluconeogenesis, and lipid stores for the release of fatty acids. In addition, appropriate activities of key enzymes governing glucose homeostasis are required (see Fig. 87-1 in Chapter 87).

**In Older Infants and Children**

Hypoglycemia in older infants and children is analogous to that of adults, in whom glucose homeostasis is maintained by glycogenolysis in the immediate postfeeding period and by gluconeogenesis several hours after meals. The liver of a 10 kg child contains 20–25 g of glycogen, which is sufficient to meet normal glucose requirements of 4–6 mg/kg/min for only 6–12 hr. Beyond this period, hepatic gluconeogenesis must be activated. Both glycogenolysis and gluconeogenesis depend on the metabolic pathway summarized in Figure 87-1. Defects in gluconeogenesis or gluconeogenesis may not be manifested in infants until the frequent feeding at 3–4 hr intervals ceases and infants sleep through the night, a situation usually present by 3–6 mo of age. The source of gluconeogenic precursors is derived primarily from muscle protein. The muscle bulk of infants and small children is substantially smaller relative to body mass than that of adults, whereas glucose requirements/unit of body mass are greater in children, so the ability to compensate for glucose deprivation by gluconeogenesis is more limited in infants and young children, as is the ability to withstand fasting for prolonged periods. The ability of muscle to generate alanine, the principal gluconeogenic amino acid, may also be limited. Thus, in normal young children, the blood glucose level falls after 24 hr of fasting, insulin concentrations fall appropriately to levels of <5–10 µU/mL, lipolysis and ketogenesis are activated, and ketones may appear in the urine.

The switch from glycogen synthesis during and immediately after meals to glycogen breakdown and later gluconeogenesis is governed by hormones, of which insulin is of central importance. Plasma insulin concentrations increase to peak levels of 5–10-fold greater than their baseline of approximately 5–10 µU/mL after meals, which serve to lower the blood glucose concentration through the activation of glycogen synthesis, enhancement of peripheral glucose uptake, and inhibition of glucose production. In addition, lipogenesis is stimulated, whereas lipolysis and ketogenesis are curtailed. During fasting, plasma insulin concentrations fall to ≤5–10 µU/mL, and together with the rise of counterregulatory hormones, this fall in insulin results in activation of gluconeogenic pathways (see Fig. 87-1). Fasting glucose concentrations are maintained through the activation of glycogenolysis and gluconeogenesis, inhibition of glycogen synthesis, and activation of lipolysis and ketogenesis. It should be emphasized that a plasma insulin concentration of >5 µU/mL, in association with a blood glucose concentration of 550–55 mg/dL (2.8–3.0 mM), is abnormal, indicating a state of excessive insulin action, here termed hyperinsulinism, because of failure of the mechanisms that normally result in suppression of insulin secretion during fasting or hypoglycemia.

The hypoglycemic effects of insulin are opposed by the actions of several hormones whose concentration in plasma increases as blood glucose falls. These counterregulatory hormones—glucagon, growth hormone, cortisol, and epinephrine—act in concert by increasing blood glucose concentrations via activating glycogenolytic enzymes (glucagon, epinephrine); inducing gluconeogenic enzymes (glucagon, cortisol); inhibiting glucose uptake by muscle (epinephrine, growth hormone, cortisol); mobilizing amino acids from muscle for gluconeogenesis (cortisol); activating lipolysis and thereby providing glycerol for gluconeogenesis and fatty acids for ketogenesis (epinephrine, cortisol, growth hormone, glucagon); and inhibiting insulin release and promoting growth hormone and glucagon secretion (epinephrine).

Congenital or acquired deficiency of any one of these hormones is uncommon but will result in hypoglycemia, which occurs when endogenous glucose production cannot be mobilized to meet energy needs in the postabsorptive state, that is, 8–12 hr after meals or during fasting. Concurrent deficiency of several hormones (hypopituitarism) may result in hypoglycemia that is more severe or appears earlier during fasting than that seen with isolated hormone deficiencies. Most of the causes of hypoglycemia in neonates, infants and children reflect inappropriate adaptation to fasting as a result of excess insulin action, or inadequate counter-regulatory hormone response primarily of cortisol and growth hormone, or enzymatic defects in the mechanisms for glycogen storage and release, or defects in gluconeogenesis.

**CLINICAL MANIFESTATIONS**

See Chapter 107.

Clinical features generally fall into 2 categories. The first includes symptoms associated with the activation of the autonomic nervous system and epinephrine release, usually seen with a rapid decline in blood glucose concentration (Table 92-1). The second category includes
symptoms caused by decreased cerebral glucose utilization (cerebral glucopenia), usually associated with a slow decline in blood glucose level or prolonged hypoglycemia (Table 92-1). Although these classic symptoms occur in older children, the symptoms of hypoglycemia in newborns and infants may be subtler and include cyanosis, apnea, hypothermia, hypotonia, poor feeding, lethargy, and seizures. Some of these symptoms may be so mild that they are missed. Occasionally, hypoglycemia may be asymptomatic in the immediate newborn period. Newborns with hyperinsulinism are often large for gestational age; older infants with hyperinsulinism may eat excessively because of chronic hypoglycemia and become obese. In childhood, hypoglycemia may present as behavior problems, inattention, hyperactivity, or seizures. It may be misdiagnosed as epilepsy, inebriation, personality disorders, headache, incoordination, and developmental delay. A blood glucose determination should always be performed in sick neonates, infants, and children (Table 92-2).

**Table 92-1** Manifestations of Hypoglycemia in Childhood

<table>
<thead>
<tr>
<th>FEATURES ASSOCIATED WITH ACTIVATION OF AUTONOMIC NERVOUS SYSTEM AND EPINEPHRINE RELEASE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety†</td>
</tr>
<tr>
<td>Perspiration†</td>
</tr>
<tr>
<td>Palpitation (tachycardia)†</td>
</tr>
<tr>
<td>Palor†</td>
</tr>
<tr>
<td>Tremulousness†</td>
</tr>
<tr>
<td>Weakness</td>
</tr>
<tr>
<td>Hunger</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Emsis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FEATURES ASSOCIATED WITH CEREBRAL GLUCOPENIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache‡</td>
</tr>
<tr>
<td>Mental confusion‡</td>
</tr>
<tr>
<td>Visual disturbances (↓ acuity, diplopia)‡</td>
</tr>
<tr>
<td>Organic personality changes‡</td>
</tr>
<tr>
<td>Inability to concentrate‡</td>
</tr>
<tr>
<td>Dysarthria</td>
</tr>
<tr>
<td>Staring</td>
</tr>
<tr>
<td>Paresthesias</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Amnesia</td>
</tr>
<tr>
<td>Ataxia, incoordination</td>
</tr>
<tr>
<td>Refusal to feed‡</td>
</tr>
<tr>
<td>Somnolence, lethargy‡</td>
</tr>
<tr>
<td>Seizures‡</td>
</tr>
<tr>
<td>Coma</td>
</tr>
<tr>
<td>Stroke, hemiplegia, aphasia</td>
</tr>
<tr>
<td>Decerebrate or decorticate posture</td>
</tr>
</tbody>
</table>

*Some of these features will be attenuated if the patient is receiving β-adrenergic blocking agents.
†Common.
‡Most common manifestations in the newborn.

Frequently, a clustering of episodic symptoms may be noted. Because these clinical manifestations may result from various causes, it is critical to measure serum glucose levels and determine whether symptoms disappear with the administration of sufficient glucose to raise the blood glucose to normal levels; if they do not, other diagnoses must be considered.

**CLASSIFICATION OF HYPOGLYCEMIA IN INFANTS AND CHILDREN**

Classification is based on knowledge of the control of glucose homeostasis in infants and children (Table 92-2).

**Neonatal, Transient, Small for Gestational Age, and Premature Infants**

See Chapter 107.

The estimated incidence of symptomatic hypoglycemia in newborns is 1-3 in 1,000 live births. This incidence is increased severalfold in certain high-risk neonatal groups (see Table 92-2 and Fig. 92-1). The prematurity and small for gestational age (SGA) infants are vulnerable to the development of hypoglycemia. The factors responsible for the high frequency of hypoglycemia in this group, as well as in other groups outlined in Table 92-2, are related to the inadequate stores of liver glycogen, muscle protein, and body fat needed to sustain the substrates required to meet energy needs. These infants are small by virtue of prematurity or impaired placental transfer of nutrients. Their enzyme systems for gluconeogenesis may not be fully developed. Transient hyperinsulinism responsive to diazoxide has also been reported as contributing to hypoglycemia in asphyxiated, SGA, and premature newborn infants. This form of hyperinsulinism associated with perinatal asphyxia, intrapartum growth restriction, maternal toxemia and other perinatal stressors, is probably the most common cause of hyperinsulinemic hypoglycemia in neonates and may be quite severe. In most cases, the condition resolves quickly, but it may persist to 7 mo of life or longer.

In contrast to deficiency of substrates or enzymes, the hormonal system appears to be functioning normally at birth in most low-risk neonates. Despite hypoglycemia, plasma concentrations of alanine, lactate, and pyruvate are higher, implying their diminished rate of utilization as substrates for gluconeogenesis. Infusion of alanine elicits further glucagon secretion but causes no significant rise in glucose. During the initial 24 hr of life, plasma concentrations of acetocetate and β-hydroxybutyrate are lower in SGA infants than in full-term infants, implying diminished lipid stores, diminished fatty acid mobilization, impaired ketogenesis, or a combination of these.
conditions. Diminished lipid stores are most likely because fat (triglyceride) feeding of newborns results in a rise in the plasma levels of glucose, ketones such as β-OH butyrate and FFA. For infants with perinatal asphyxia, and some SGA newborns who have transient hyperinsulinism, hypoglycemia and diminished concentrations of β-OH butyrate and FFAs are the hallmark of hyperinsulinism.

The role of FFAs and their oxidation in stimulating neonatal gluconeogenesis is essential. The provision of FFAs as triglyceride feedings from formula or human milk together with gluconeogenic precursors may prevent the hypoglycemia that usually ensues after neonatal fasting. For these and other reasons, milk feedings are introduced early (at birth or within 2-4 hr) after delivery. In the hospital setting, when feeding is precluded by virtue of respiratory distress or when feedings alone cannot maintain blood glucose concentrations at levels >50 mg/dL, intravenous glucose at a rate that supplies 4-8 mg/kg/min should be started. Infants with transient neonatal hypoglycemia can usually maintain the blood glucose level spontaneously after 2-3 days of life, but some require longer periods of support. In these latter infants,
insulin values >5 µU/mL at the time of hypoglycemia should be treated with diazoxide.

**Infants Born to Diabetic Mothers**

See Chapter 107.1.

Of the transient hyperinsulinemic states, infants born to diabetic mothers are the most common. Gestational diabetes affects some 2% of pregnant women, and ~1 in 1,000 pregnant women have insulin-dependent diabetes. At birth, infants born to these mothers may be large and plethoric, and their body stores of glycogen, protein, and fat are replete.

Hypoglycemia in infants of diabetic mothers is mostly related to hyperinsulinemia and partly related to diminished glucagon secretion. Hypertrophy and hyperplasia of the islets is present, as is a brisk, biphasic, and typically mature insulin response to glucose; this brisk insulin response is absent in normal infants. Infants born to diabetic mothers also have a subnormal surge in plasma glucagon immediately after birth, subnormal glucagon secretion in response to stimuli, and, initially, excessive sympathetic activity that may lead to adrenomedullary exhaustion as reflected by decreased urinary excretion of epinephrine. The normal plasma hormonal pattern of low insulin, high glucagon, and high catecholamines is reversed to a pattern of high insulin, low glucagon, and low epinephrine. As a consequence of this abnormal hormonal profile, endogenous glucose production is significantly inhibited compared with that in normal infants, thus predisposing them to hypoglycemia.

Mothers whose diabetes has been well controlled during pregnancy, labor, and delivery generally have infants near normal size who are less likely to develop neonatal hypoglycemia and other complications formerly considered typical of such infants (see Chapter 107.1). In supplying exogenous glucose to these hypoglycemic infants, it is important to avoid hyperglycemia that evokes a prompt exuberant insulin release, which may result in rebound hypoglycemia. When needed, glucose should be provided at continuous infusion rates of 4-8 mg/kg/min, but the appropriate dose for each patient must be individually adjusted.

During labor and delivery, maternal hyperglycemia should be avoided because it results in fetal hyperglycemia, which predisposes to hypoglycemia when the glucose supply is interrupted at birth. Hypoglycemia persisting or occurring after 1 wk of life requires an evaluation for the causes listed in Table 92-2.

Infants born with erythroblastosis fetalis may also have hyperinsulinemia and share many physical features, such as large body size, with infants born to diabetic mothers. The cause of the hyperinsulinemia in infants with erythroblastosis is not clear.

**PERSISTENT OR RECURRENT HYPOGLYCEMIA IN INFANTS AND CHILDREN**

**Hyperinsulinism**

Most children with hyperinsulinism that causes hypoglycemia present in the neonatal period or later in infancy; hyperinsulinism is the most common cause of persistent hypoglycemia in early infancy. Infants who have hyperinsulinism may be macrometric at birth, with the anabolic effects of insulin in utero. There is no history or biochemical evidence of maternal diabetes. The onset of symptoms is from birth to 18 mo of age, but occasionally it only becomes evident in older children. Insulin concentrations are appropriately elevated at the time of documented hypoglycemia; with nonhyperinsulinemic hypoglycemia, plasma insulin concentrations should be <5 µU/mL and no higher than 10 µU/mL. In affected infants, plasma insulin concentrations at the time of hypoglycemia are commonly >5-10 µU/mL. Some authorities set more stringent criteria, arguing that any value of insulin >2 µU/mL with hypoglycemia is abnormal. The insulin (µU/mL)/glucose (mg/dL) ratio is commonly >0.4; plasma insulin-like growth factor binding protein-1 (IGFBP-1), β OH butyrate, and FFA levels are low with hyperinsulinism. Rare instances of activating mutations in the insulin receptor signaling pathway have been reported where the clinical and biochemical features are similar to states of excessive insulin secretion, yet insulin concentrations are low to the point of being undetectable. Hence, the preferred term is hyperinsulinism, to describe a state of increased insulin action. Macroscopic infants may present with hypoglycemia from the first days of life. Infants with lesser degrees of hyperinsulinism may manifest hypoglycemia only after the first few weeks to months, when the frequency of feedings has been decreased to permit the infant to sleep through the night, and hyperinsulinism prevents the mobilization of endogenous glucose. Increasing appetite and demands for feeding, wilting spells, jitteriness, and frank seizures are the most common presenting features. Additional clues include the rapid development of fasting hypoglycemia within 4-8 hr of food deprivation compared with other causes of hypoglycemia (Tables 92-3 and 92-4); the need for high rates of exogenous glucose infusion to prevent hypoglycemia, often at rates >10-15 mg/kg/min; the absence of ketonemia or acidosis; and elevated C-peptide or proinsulin levels at the time of hypoglycemia. The latter insulin-related products are absent in factitious hypoglycemia from exogenous administration of insulin as a form of child abuse (Munchausen by proxy syndrome; see Chapter 40.2). Hypoglycemia is invariably provoked by withholding feedings for several hours, permitting simultaneous measurement of glucose, insulin, ketones, and FFAs in the same sample at the time of clinically manifested hypoglycemia. This is termed the critical sample. The glycemnic response to glucagon at the time of hypoglycemia reveals a brisk increment in glucose concentration of at least 40 mg/dL, which implies that glucose mobilization has been restrained by insulin but that glycogenolytic mechanisms are intact (Tables 92-5, 92-6, and 92-7).

The measurement of serum IGFBP-1 concentration may help diagnose hyperinsulinism. The secretion of IGFBP-1 is acutely inhibited by insulin action; IGFBP-1 concentrations are low during hyperinsulinism-induced hypoglycemia. In patients with spontaneous or fasting-induced hypoglycemia with a low insulin level (ketotic hypoglycemia, normal fasting), IGFBP-1 concentrations are significantly higher. The differential diagnosis of endogenous hyperinsulinism includes diffuse β-cell hyperplasia or focal β-cell microadenoma.

The distinction between these 2 major entities is important because the latter, if unresponsive to medical therapy, requires near total pancreatectomy, despite which hypoglycemia may persist or diabetes mellitus may ensue at some later time. Some affected infants may respond to sirolimus. By contrast, focal adenomas diagnosed

<table>
<thead>
<tr>
<th>Table 92-3</th>
<th>Hypoglycemia in Infants and Children: Clinical and Laboratory Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>GROUP</td>
<td>AGE AT DIAGNOSIS (mo)</td>
</tr>
<tr>
<td>HYPERINSULINEMIA (N = 12)</td>
<td>Mean 7.4</td>
</tr>
<tr>
<td></td>
<td>SEM 2.0</td>
</tr>
<tr>
<td>NONHYPERINSULINEMIA (N = 16)</td>
<td>Mean 41.8</td>
</tr>
<tr>
<td></td>
<td>SEM 7.3</td>
</tr>
</tbody>
</table>

*In hypoglycemia caused by hyperinsulinism β OH butyrate and FFA are low compared with normal at same duration of fasting.
†Milder forms of hyperinsulinism may require up to 18 hr of fasting to provoke hypoglycemia.
SEM, standard error of mean.
### Table 92-4: Correlation of Clinical Features with Molecular Defects in Persistent Hyperinsulinemic Hypoglycemia in Infancy

<table>
<thead>
<tr>
<th>TYPE</th>
<th>MACROSOMIA</th>
<th>HYPOGLYCEMIA/HYPERINSULINEMIA</th>
<th>FAMILY HISTORY</th>
<th>MOLECULAR DEFECTS</th>
<th>ASSOCIATED CLINICAL, BIOCHEMICAL, OR MOLECULAR FEATURES</th>
<th>RESPONSE TO MEDICAL MANAGEMENT</th>
<th>RECOMMENDED SURGICAL APPROACH</th>
<th>PROGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic</td>
<td>Present at birth</td>
<td>Moderate/severe in first days to weeks of life</td>
<td>Negative</td>
<td>? SUR/K_{IR} 6.2 Mutations not always identified in diffuse hyperplasia</td>
<td>Loss of heterozygosity in microadenomatous tissue</td>
<td>Generally poor; may respond better to somatostatin than to diazoxide</td>
<td>Partial pancreatectomy if frozen section shows β-cell crowding with small nuclei—suggests microadenoma</td>
<td>Subtotal &gt;95% pancreatectomy if frozen section shows giant nuclei in β-cells—suggests diffuse hyperplasia</td>
</tr>
<tr>
<td>Autosomal recessive</td>
<td>Present at birth</td>
<td>Severe in first days to weeks of life</td>
<td>Positive</td>
<td>SUR/K_{IR} 6.2</td>
<td>Consanguinity a feature in some populations</td>
<td>Poor</td>
<td>Subtotal pancreatectomy</td>
<td>Guarded</td>
</tr>
<tr>
<td>Autosomal dominant</td>
<td>Unusual</td>
<td>Moderate onset usually post 6 mo of age</td>
<td>Positive</td>
<td>Glucokinase (activating) Some cases gene unknown</td>
<td>None</td>
<td>Very good to excellent</td>
<td>Surgery usually not required</td>
<td>Partial pancreatectomy only if medical management fails</td>
</tr>
<tr>
<td>Autosomal dominant</td>
<td>Unusual</td>
<td>Moderate onset usually post 6 mo of age</td>
<td>Positive</td>
<td>Glutamate dehydrogenase (activating)</td>
<td>Modest hyperammonemia</td>
<td>Very good to excellent</td>
<td>Surgery usually not required</td>
<td>Excellent</td>
</tr>
<tr>
<td>Beckwith-Wiedemann syndrome</td>
<td>Present at birth</td>
<td>Moderate, spontaneously resolves post 6 mo of age</td>
<td>Negative</td>
<td>Duplicating/imprinting in chromosome 11p15.1</td>
<td>Macroglossia, omphalocele, hemihypertrophy</td>
<td>Good</td>
<td>Not recommended</td>
<td>Excellent for hypoglycemia; guarded for possible development of embryonal tumors (Wilms hepatoblastoma)</td>
</tr>
<tr>
<td>Congenital disorders of glycosylation</td>
<td>Not usual</td>
<td>Moderate/onset post 3 mo of age</td>
<td>Negative</td>
<td>Phosphomannose isomerase deficiency</td>
<td>Hepatomegaly, vomiting, intractable diarrhea</td>
<td>Good with mannose supplement</td>
<td>Not recommended</td>
<td>Fair</td>
</tr>
</tbody>
</table>

**Notes:**
- **SUR/K_{IR} 6.2:** Suramin kinetics.
- **Macroglossia, omphalocele, hemihypertrophy:** Symptoms of Beckwith-Wiedemann syndrome.
activating mutation of glutamate dehydrogenase.

A variety of genetic defects responsible for abnormalities in the endocrine pancreas characterized by autonomous insulin secretion that is invasive and technically difficult procedures have been largely abandoned, in favor of positron emission tomography using 18-fluoro-L-dopa. This technique can distinguish the diffuse form (uniform fluorescence throughout the pancreas) from the focal form (focal uptake of 18-fluoro-L-dopa and localized fluorescence) with an extremely high degree of reliability, success, specificity, and sensitivity (see Fig. 92-3 and below). Insulin-secreting macroadenomas are rare in childhood and may be diagnosed preoperatively via CT or MRI. The plasma levels of insulin alone, however, cannot distinguish the aforementioned entities. The diffuse or microadenomatous forms of islet cell hyperplasia represent a variety of genetic defects responsible for abnormalities in the endocrine pancreas characterized by autonomous insulin secretion that is not appropriately reduced when blood glucose declines spontaneously or in response to provocative maneuvers such as fasting (see Tables 92-4, 92-7, and 92-8 and Fig. 92-2). Clinical, biochemical, and molecular genetic approaches now permit classification of congenital hyperinsulinism, formerly termed nesidioblastosis, into distinct entities. Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) may be inherited or sporadic, is severe, and is caused by mutations that affect the regulation of the potassium channel intimately involved in insulin secretion by the pancreatic β cell (Fig. 92-2). Normally, glucose entry into the β cell is enabled by the non–insulin-responsive glucose transporter GLUT-2. On entry, glucose is phosphorylated to glucose-6-phosphate by the enzyme glucokinase, enabling glucose metabolism through overproduction of ATP which causes hyperinsulinism. Genetic defects in fatty acid metabolism, in the insulin transcription factor HNF-4α and HNF-1α, and in the uncoupling protein UCP-2 of the mitochondrial gene complex also have been involved in

### Table 92-5

<table>
<thead>
<tr>
<th>SUBSTRATES</th>
<th>Analysis of Critical Blood Sample During Hypoglycemia and 30 Minutes After Glucagon*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td></td>
</tr>
<tr>
<td>Free fatty acids</td>
<td></td>
</tr>
<tr>
<td>Ketones</td>
<td></td>
</tr>
<tr>
<td>Lactate</td>
<td></td>
</tr>
<tr>
<td>Uric acid</td>
<td></td>
</tr>
<tr>
<td>Ammonia</td>
<td></td>
</tr>
<tr>
<td>HORMONES</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
</tr>
<tr>
<td>Cortisol</td>
<td></td>
</tr>
<tr>
<td>Growth hormone</td>
<td></td>
</tr>
<tr>
<td>Thyroxine, thyroid-stimulating hormone</td>
<td></td>
</tr>
<tr>
<td>Insulin-like growth factor binding protein-1*</td>
<td></td>
</tr>
</tbody>
</table>

*Glucagon 50 µg/kg with maximum of 1 mg IV or IM.

Measures once only before or after glucagon administration. Rise in glucose of ≥40 mg/dL after glucagon given at the time of hypoglycemia strongly suggests a hyperinsulinemic state with adequate hepatic glycogen stores and intact glycogenolytic enzymes. If ammonia is elevated to 100-200 µM, consider activating mutation of glutamate dehydrogenase.

### Table 92-6

<table>
<thead>
<tr>
<th>Criteria for Diagnosing Hyperinsulinism Based on “Critical” Samples (Drawn at a Time of Fasting Hypoglycemia: Plasma Glucose &lt;50 mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hyperinsulinemia (plasma insulin ≥2 µU/mL)*</td>
</tr>
<tr>
<td>2. Hypoglycemia (plasma free fatty acids &lt;1.5 mmol/L)</td>
</tr>
<tr>
<td>3. Hypoketoneemia (plasma β-hydroxybutyrate: &lt;2.0 mmol/L)</td>
</tr>
<tr>
<td>4. Inappropriate glycemic response to glucagon, 1 mg IV (change in glucose ≥40 mg/dL)</td>
</tr>
</tbody>
</table>


### Table 92-7

<table>
<thead>
<tr>
<th>Diagnosis of Acute Hypoglycemia in Infants and Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACUTE SYMPTOMS PRESENT</td>
</tr>
<tr>
<td>1. Obtain blood sample before and 30 min after glucagon administration.</td>
</tr>
<tr>
<td>2. Obtain urine as soon as possible. Examine for ketones; if not present and hypoglycemia confirmed, suspect hyperinsulinemia or fatty acid oxidation defect; if present, suspect ketotic, hormone deficiency, inborn error of glycogen metabolism, or defective glucogenogenesis.</td>
</tr>
<tr>
<td>3. Measure glucose in the original blood sample. If hypoglycemia is confirmed, proceed with substrate-hormone measurement as in Table 92-5.</td>
</tr>
<tr>
<td>4. If glycemic increment after glucagon exceeds 40 mg/dL above basal, suspect hyperinsulinemia.</td>
</tr>
<tr>
<td>5. If insulin level at time of confirmed hypoglycemia is ≥5 µU/mL, suspect endogenous hyperinsulinemia; if &gt;100 µU/mL, suspect factitious hyperinsulinemia (exogenous insulin injection). Admit to hospital for supervised fast.</td>
</tr>
<tr>
<td>6. If cortisol is &lt;10 µg/dL or growth hormone is &lt;5 ng/mL, or both, suspect adrenal insufficiency or pituitary disease, or both. Admit to hospital for hormonal testing and neuroimaging.</td>
</tr>
</tbody>
</table>

### HISTORY SUGGESTIVE: ACUTE SYMPTOMS NOT PRESENT

2. Careful examination for hepatomegaly (glycogen storage disease; defect in glucogenogenesis); pigmentation (adrenal failure), stature and neurologic status (pituitary disease).
3. Admit to hospital for provocative testing:
   a. 24 hr fast under careful observation; when symptoms provoked, proceed with steps 1-4 as when acute symptoms present.
   b. Pituitary–adrenal function using arginine-insulin stimulation test if indicated.
4. Consider molecular diagnostic test before liver biopsy for histologic and enzyme determinations.
5. Oral glucose tolerance test (1.75 g/kg; max 75 g) if reactive hypoglycemia suspected (dumping syndrome, etc.).
<table>
<thead>
<tr>
<th>Condition</th>
<th>Hypoglycemia</th>
<th>Urinary Ketones or Reducing Sugars</th>
<th>Hepatomegaly</th>
<th>Serum</th>
<th>URIC ACID</th>
<th>GLUCOSE</th>
<th>INSULIN</th>
<th>KETONES</th>
<th>ALANINE</th>
<th>LACTATE</th>
<th>Glycemic Response to Glucagon</th>
<th>Glycemic Response to Infusion of</th>
<th>Details of each condition are discussed in the text. 0, absence; ↑ or ↓ indicates respectively small increase or decrease; †† or †† indicates respectively large increase or decrease.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Normal</td>
<td>Normal</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>Normal</td>
<td>Normal</td>
<td>Not indicated</td>
<td></td>
</tr>
<tr>
<td>Hyperinsulinemia</td>
<td>Recurrent</td>
<td>0</td>
<td>0</td>
<td>Normal</td>
<td>Normal</td>
<td>↓↓</td>
<td>↑↑</td>
<td>↓↓</td>
<td>Normal</td>
<td>Normal</td>
<td>↑ ↑</td>
<td>Not indicated</td>
<td></td>
</tr>
<tr>
<td>Ketotic hypoglycemia</td>
<td>Severe with missed meals</td>
<td>Ketonuria +++</td>
<td>0</td>
<td>Normal</td>
<td>Normal</td>
<td>↓↓</td>
<td>↓</td>
<td>↑↑</td>
<td>↓↓</td>
<td>Normal</td>
<td>↑ ↓</td>
<td>Not indicated</td>
<td></td>
</tr>
<tr>
<td>Fatty acid oxidation disorder</td>
<td>Severe with missed meals</td>
<td>Absent</td>
<td>0 to + Abnormal liver function test results</td>
<td>Abnormal</td>
<td>↑</td>
<td>Contraindicated</td>
<td>↑ ↓</td>
<td>Not indicated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>Moderate with missed meals</td>
<td>Ketonuria ++</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>↓↓</td>
<td>↓</td>
<td>↑↑</td>
<td>↓↓</td>
<td>Normal</td>
<td>↑ ↓</td>
<td>↑ ↑</td>
<td></td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>Severe with missed meals</td>
<td>Ketonuria ++</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>↓↓</td>
<td>↓</td>
<td>↑↑</td>
<td>↓↓</td>
<td>Normal</td>
<td>↑ ↓</td>
<td>↑ ↑</td>
<td></td>
</tr>
<tr>
<td>Enzyme deficiencies</td>
<td>Severe-constant</td>
<td>Ketonuria +++</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↓↓</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>0</td>
<td>0-↓↓</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose-6-phosphatase debrancher</td>
<td>Moderate with fasting</td>
<td>++</td>
<td>++</td>
<td>Normal</td>
<td>Normal</td>
<td>↓↓</td>
<td>↓</td>
<td>↑↑</td>
<td>↓↓</td>
<td>Normal</td>
<td>↑ 0-↓↓</td>
<td>↑ ↑</td>
<td></td>
</tr>
<tr>
<td>Phosphorylase</td>
<td>Mild-moderate</td>
<td>Ketonuria ++</td>
<td>+</td>
<td>Normal</td>
<td>Normal</td>
<td>↓</td>
<td>↓</td>
<td>↑↑</td>
<td>↓↓</td>
<td>Normal</td>
<td>0-↑ 0-↓↓</td>
<td>↑ ↑</td>
<td></td>
</tr>
<tr>
<td>Fructose-1,6-diphosphatase</td>
<td>Severe with fasting</td>
<td>Ketonuria +++</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↓↓</td>
<td>↓</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>0-↓↓</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Galactosemia</td>
<td>After milk or milk products</td>
<td>0 Ketones,(s)</td>
<td>+++</td>
<td>Normal</td>
<td>Normal</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>Normal</td>
<td>↑ 0-↓↓</td>
<td>↑ ↑</td>
<td></td>
</tr>
<tr>
<td>Fructose intolerance</td>
<td>After fructose</td>
<td>0 Ketones,(s)</td>
<td>+++</td>
<td>Normal</td>
<td>Normal</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>Normal</td>
<td>↑ 0-↓↓</td>
<td>↑ ↑</td>
<td></td>
</tr>
</tbody>
</table>
hyperinsulinemic hypoglycemia. Inactivating mutations of the glucokinase gene or activating mutations of the ATP-regulated potassium channel which prevent or limit closure of the channel, are responsible for inadequate insulin secretion and form the basis of some forms of maturity-onset diabetes of youth or of neonatal diabetes mellitus (see Chapter 589).

The familial forms of PHHI are more common in certain populations, notably Arabic and Ashkenazi Jewish communities, where it may reach an incidence of approximately 1 in 2,500, compared with the sporadic rates in the general population of approximately 1 in 50,000. These autosomal recessive forms of PHHI typically present in the immediate newborn period as macrosomic newborns with a weight frequently >4.0 kg and severe recurrent or persistent hypoglycemia manifesting in the initial hours or days of life. Glucose infusions as high as 15-20 mg/kg/min and frequent feedings fail to maintain euglycemia. Diazoxide, which acts by opening K<sub>ATP</sub> channels (see Fig. 92-2) fails to control hypoglycemia adequately. Somatostatin (octreotide), which also opens K<sub>ATP</sub> channels and inhibits calcium flux, may be partially effective in approximately 50% of patients (see Fig. 92-2). Calcium channel blocking agents have had inconsistent effects. Some affected infants have responded to sirolimus. When affected patients are unresponsive to these measures, pancreatectomy is strongly recommended to avoid the long-term neurologic sequelae of hypoglycemia. If surgery is undertaken, preoperative CT or MRI rarely reveals an isolated adenoma, which would then permit local resection. Intraoperative ultrasonography may identify a small impalpable adenoma, permitting local resection. Adenomas often present in late infancy or early childhood.

Distinguishing between focal and diffuse cases of persistent hyperinsulinism has been attempted in several ways. Preoperatively, transhepatic portal vein catheterization and selective pancreatic venous sampling to measure insulin may localize a focal lesion from the hepatic portal vein catheterization and selective pancreatic venous concentration (arterial stimulation-venous sampling) may localize a focal lesion. Both approaches are highly invasive, restricted to specialized centers, and not uniformly successful in distinguishing the focal from the diffuse forms, hence, these techniques are not recommended. 18F-labeled l-dopa combined with positron emission tomography scanning is a highly promising means to distinguish the focal from the diffuse forms of persistent hyperinsulinism unresponsive to medical management (Fig. 92-3). The “gold standard” remains intraoperative histologic characterization. Diffuse hyperinsulinism is characterized by large β cells with abnormally large nuclei, whereas focal adenomatous lesions display small and normal β cell nuclei. Although SUR1 mutations are present in both types, the focal lesions arise by a random loss of a maternally imprinted growth-inhibitory gene on maternal chromosome 11p in association with paternal transmission of a mutated 11p in association with paternal transmission of a mutated SUR1(Kir 6.2) paternal chromosome 11p expressing the insulin-like growth factor 2 (IGF2) gene. Thus the focal form represents a double hit—loss of maternal repressor and transmission of a paternal mutation that contains a growth-promoting gene. Local excision of focal adenomatous islet cell hyperplasia results in a cure with little or no recurrence. For the diffuse form, near-total resection of 85-90% of the pancreas is recommended. The near-total pancreatectomy required for the diffuse

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**Figure 92-2** Schematic of the pancreatic cell with some important steps in insulin secretion. The membrane-spanning, adenosine triphosphate (ATP)-sensitive potassium (K<sup>+</sup>) channel (K<sub>ATP</sub>) consists of 2 subunits: the sulfonylurea receptor (SUR) and the inward rectifying K channel (K<sub>IR</sub> 6.2). In the resting state, the ratio of ATP to adenosine diphosphate (ADP) maintains K<sub>ATP</sub> in an open state, permitting efflux of intracellular K<sup>+</sup>. When blood glucose concentration rises, its entry into the β cell is facilitated by the GLUT-2 glucose transporter, a process not regulated by insulin. Within the β cell, glucose is converted to glucose-6-phosphate by the enzyme glucokinase and then undergoes metabolism to generate energy. The resultant increase in ATP relative to ADP closes K<sub>ATP</sub>, preventing efflux of K<sup>+</sup>, and the rise of intracellular K<sup>+</sup> depolarizes the cell membrane and opens a calcium (Ca<sup>2+</sup>) channel. The intracellular rise in Ca<sup>2+</sup> triggers insulin secretion via exocytosis. Sulfonylureas trigger insulin secretion by reacting with their receptor (SUR) to close K<sub>ATP</sub>; diazoxide inhibits this process, whereas somatostatin, or its analog octreotide, inhibits insulin secretion by interfering with calcium influx. Genetic mutations in SUR1 or K<sub>IR</sub> 6.2 that prevent K<sub>ATP</sub> from being open, tonically maintain inappropriate insulin secretion and are responsible for autosomal recessive forms of persistent hyperinsulinemic hypoglycemia of infancy (PHHI). One form of autosomal dominant PHHI is caused by an activating mutation in glucokinase. The amino acid leucine also triggers insulin secretion by closure of K<sub>ATP</sub>. Metabolism of leucine is facilitated by the enzyme glutamate dehydrogenase (GDH), and overactivity of this enzyme in the pancreas leads to hyperinsulinemia with hypoglycemia, associated with hyperammonemia from overactivity of GDH in the liver. Mutations in the pyruvate channel SLC16A1 can cause eutopic expression in the β cell and permit pyruvate, accumulated during exercise, to induce insulin secretion and hence exercise-induced hypoglycemia. Mutations in the mitochondrial uncoupling protein 2 (UCP2) and hydroxyl acyl-CoA dehydrogenase (HADH) are associated with hyperinsulinism (HI) by mechanisms yet to be defined. Mutations in the transcription factors hepatic nuclear factors (HNF) 4α and 1α can be associated with neonatal macrosomia and HI, but progress to monogenic diabetes of youth (MODY) later in life. √_† stimulation; GTP, guanosine triphosphate; X, inhibition.
Figure 92-3 Congenital hyperinsulinism. I Panels (diffuse): [18F]-DOPA positron emission tomography (PET) of patient with diffuse form of congenital hyperinsulinism. A, Diffuse uptake of [18F]-DOPA is visualized throughout the pancreas. Transverse views show (B) normal pancreatic tissue on abdominal CT; (C) diffuse uptake of [18F]-DOPA in pancreas; and (D) confirmation of pancreatic uptake of [18F]-DOPA with coregistration. H, head of pancreas; T, tail of pancreas. II Panels (focal): [18F]-DOPA PET of patient with focal form of congenital hyperinsulinism. A, Discrete area of increased [18F]-DOPA uptake is visualized in the head of the pancreas. The intensity of this area is greater than that observed in the liver and neighboring normal pancreatic tissue. Transverse views show (B) normal pancreatic tissue on abdominal CT; (C) focal uptake of [18F]-DOPA in pancreatic head; and (D) confirmation of [18F]-DOPA uptake in the pancreatic head with coregistration. (Courtesy of Dr. Olga Hardy, Children’s Hospital of Philadelphia.)
hyperplastic lesions is, however, often associated with persistent hypoglycemia with the later development of hyperglycemia or frank, insulin-requiring diabetes mellitus.

Further resection of the remaining pancreas may occasionally be necessary if hypoglycemia recurs and cannot be controlled by medical measures, such as the use of octreotide or diazoxide.

Experienced pediatric surgeons in medical centers equipped to provide the necessary preoperative and postoperative care, diagnostic evaluation, and management should perform surgery. In some patients who have been managed medically, hyperinsulinism and hypoglycemia regress over months. This is similar to what occurs in children with the hyperinsulinemic hypoglycemia seen in the epigenetic and genetic imprinting disorders. **Beckwith-Wiedemann syndrome.**

If hypoglycemia first manifests between 3 and 6 mo of age or later, a therapeutic trial using medical approaches with diazoxide, octreotide, and frequent feedings can be attempted for up to 2-4 wk. Failure to maintain euglycemia without undesirable side effects from the drugs may prompt the need for surgery. Some success in suppressing insulin release and correcting hypoglycemia in patients with PHHI has been reported with the use of the long-acting somatostatin analog octreotide. Most cases of neonatal PHHI are sporadic; familial forms permit genetic counseling on the basis of anticipated autosomal recessive inheritance.

A second form of familial PHHI suggests autosomal dominant inheritance. The clinical features tend to be less severe, and onset of hypoglycemia is most likely, but not exclusively, to occur beyond the immediate newborn period and usually beyond the period of weaning at an average age at onset of about 1 yr. At birth, macrosomia is rarely observed, and response to diazoxide is almost uniform. The initial presentation may be delayed and rarely occur as late as 30 yr; unless provoked by fasting. The genetic basis for this autosomal dominant form has not been delineated; it is not always linked to K\textsubscript{ATP}. The activating mutation in glucokinase is transmitted in an autosomal dominant manner. If a family history is present, genetic counseling for a 50% recurrence rate can be given for future offspring.

A third form of persistent PHHI is associated with **mild and asymptomatic hyperammonemia,** usually as a sporadic occurrence, although dominant inheritance occurs. Presentation is more like the autosomal dominant form than the autosomal recessive form. Diet and diazoxide control symptoms, but pancreatectomy may be necessary in some cases. The association of hyperinsulinism and hyperammonemia is caused by an inherited or de novo gain-of-function mutation in the enzyme glutamate dehydrogenase. The resulting increase in glutamate oxidation in the pancreatic β cell raises the ATP concentration and, hence, the ratio of ATP:adenosine diphosphate, which closes K\textsubscript{ATP}

Disorders of protein glycosylation usually present with neurologic consequences, as seen in other hyperammonemic states. Leucine, a potent amino acid for stimulating insulin secretion and implicated in leucine-sensitive hypoglycemia, acts by allosterically stimulating glutamate dehydrogenase. Thus, **leucine-sensitive hypoglycemia** may be a form of the hyperinsulinemia–hyperammonemia syndrome or a potentiation of mild disorders of the K\textsubscript{ATP} channel; it need not always be associated with a modest increase in serum ammonia.

Hyperammonemia associated with hyperinsulinemia is also seen in approximately 50% of patients with the Beckwith-Wiedemann syndrome. This syndrome is caused by an imprinting disorder (see Chapter 81) and characterized by omphalocele, gigantism, macroglossia, microcephaly, and visceromegaly (Fig. 92-4). Distinctive lateral earlobe fissures and facial nevus flammeus are present; hemihypertrophy occurs in many of these infants. Diffuse islet cell hyperplasia occurs in infants with hypoglycemia. The diagnostic and therapeutic approaches are the same as those discussed previously, although microcephaly and slowing of brain development may occur independently of hypoglycemia. Patients with the Beckwith-Wiedemann syndrome may acquire tumors, including Wilms tumor, hepatoblastoma, adrenal carcinoma, gonadoblastoma, and rhabdomyosarcoma. This overgrowth syndrome is caused by mutations in the chromosome 11p15.5 region close to the genes for insulin, SUR1, K\textsubscript{ATP}, and IGF2. Duplications in this region and genetic imprinting from a defective or absent copy of the maternally derived gene are involved in the variable features and patterns of transmission. Hyperammonia may resolve in weeks to months of medical therapy. Pancreatic resection may rarely be needed.

Hyperinsulinemic hypoglycemia in infancy is reported as a manifestation of one form of **congenital disorder of glycosylation.** Disorders of protein glycosylation usually present with neurologic symptoms but may also include liver dysfunction with hepatomegaly, intractable diarrhea, protein-losing enteropathy, and hypoglycemia (see Chapter 87.6). These disorders are often underdiagnosed. One entity associated with hyperinsulinemic hypoglycemia is caused by phosphomannomutase deficiency, and clinical improvement followed supplemental treatment with oral mannose at a dose of 0.17 g/kg 6 times per day.

After the first 12 mo of life, hyperinsulinemic states are uncommon until islet cell adenomas reappear as a cause after the patient is several years of age. Hyperinsulinemia as a result of **islet cell adenoma** should be considered in any child 5 yr or older who presents with hypoglycemia. Islet cell adenomas do not “light up” during scanning with l-dopa labeled with fluorine-18. An islet cell adenoma in a child should arouse suspicion of the possibility of multiple endocrine neoplasia type 1 (Wermer syndrome), which involves mutations in the menin gene and may be associated with hyperparathyroidism and with pituitary tumors. **Tables 92-7 and 92-8** outline the diagnostic approach. Fasting for up to 24 hr usually provokes hypoglycemia; coexisting hyperinsulinemia confirms the diagnosis,
provided that factitious administration of insulin by the parents, a form of Munchausen syndrome by proxy, is excluded. Occasionally, provocative tests may be required. Exogenously administered insulin can be distinguished from endogenous insulin by simultaneous measurement of C-peptide concentration. If C-peptide levels are elevated, endogenous insulin secretion is responsible for the hypoglycemia; if C-peptide levels are low but insulin values are high, exogenous insulin has been administered, perhaps as a form of child abuse. Islet cell adenomas at this age are treated by surgical excision. Antibodies to insulin or the insulin receptor (insulin mimetic action) are also rarely associated with hypoglycemia. Activating mutations in the Akt2 signaling complex of the insulin receptor also can cause hyperinsulinism. Some tumors produce insulin-like growth factors, thereby provoking hypoglycemia by interacting with the insulin receptor. The astute clinician must also consider the possibility of deliberate or accidental ingestion of drugs such as a sulfonylurea or related compound that stimulates insulin secretion. In such cases, insulin and C-peptide concentrations in blood will be elevated. Inadvertent substitution of an insulin secretagogue by a dispensing error should be considered in those taking medications who suddenly develop documented hypoglycemia.

A rare form of hyperinsulinemic hypoglycemia has been reported after exercise. Whereas glucose and insulin remain unchanged in most people after moderate, short-term exercise, rare patients manifest severe hypoglycemia with hyperinsulinemia 15-50 min after the same standardized exercise. This form of exercise-induced hyperinsulinism is caused by an abnormal responsiveness of β-cell insulin release in response to pyruvate generated during exercise. The gene responsible for this syndrome, SLC16A1, regulates a transporter, MCT1, that controls the entry of pyruvate into cells. Dominant mutations in SLC16A1 that increase the ectopic expression of MCT1 transporter in pancreatic β cells permit excessive entry of pyruvate into β cells and act to increase insulin secretion with resultant hypoglycemia during exercise.

Hypoglycemia with so-called nesidioblastosis has also rarely been reported after bariatric surgery for obesity. The mechanism for this form of hyperinsulinemic hypoglycemia remains to be defined.

Infants and children with Nissen fundoplication, a relatively common procedure used to ameliorate gastroesophageal reflux, frequently have an associated “dumping” syndrome with hypoglycemia. Characteristic features include significant hyperglycemia of 200 mg/dL and up to 500 mg/dL 30 min postprandially, and severe hypoglycemia (average 32 mg/dL in one series) 1.5-3.0 hr later. The early hyperglycemia phase is associated with brisk and excessive insulin release that causes the rebound hypoglycemia. A role for exaggerated GLP1 secretion has been proposed and glucagon responses have been reported to be inappropriately low in some cases. However, the physologic mechanisms are not always clearly understood, and attempted treatments not always effective; acarbose, an inhibitor of glucose absorption, was reported to be successful in one small series.

Endocrine Deficiency
Hypoglycemia associated with endocrine deficiency is usually caused by adrenal insufficiency with or without associated growth hormone deficiency (see Chapters 557 and 575). In panhypopituitarism, isolated adrenocorticotropic hormone (ACTH) or growth hormone deficiency, or combined ACTH deficiency plus growth hormone deficiency, the incidence of hypoglycemia is as high as 20%. In the newborn period, hypoglycemia may be the presenting feature of hypopituitarism; in males, a microphallus may provide a clue to a coexisting deficiency of gonadotropin. Newborns with hypopituitarism often have a form of “hepatitis” associated with cholestatic jaundice and hypoglycemia. The combination of hypoglycemia and cholestatic jaundice requires exclusion of hypopituitarism as a cause, as the jaundice resolves with replacement treatment of growth hormone, cortisol, and thyroid as required. This constellation is often associated with the syndrome of septooptic dysplasia. When adrenal disease is severe, as in congenital adrenal hyperplasia caused by enzyme defects in cortisol synthesis, adrenal hemorrhage, or congenital hypoplasia of the adrenal glands, disturbances in serum electrolytes with hyponatremia and hyperkalemia or ambiguous genitals may provide diagnostic clues (see Chapter 576). In older children, failure of growth should suggest growth hormone deficiency. Hyperpigmentation or salt-craving may provide the clue to Addison disease with increased ACTH levels or adrenal unresponsiveness to ACTH owing to a defect in the adrenal receptor for ACTH, congenital adrenal hypoplasia, adrenoleukodystrophy, or the Allgrove triple A syndrome. The frequent association of Addison disease in childhood with hypoparathyroidism (hypocalciemia), chronic mucocutaneous candidiasis, and other endocrinopathies which constitute the autoimmune polyendocrinopathy syndrome type 1 should be considered. Adrenoleukodystrophy, and congenital adrenal hypoplasia are sex-linked conditions and should be considered in the differential diagnosis of primary Addison disease in male children (see Chapter 86.2).

Hypoglycemia in cortisol–growth hormone deficiency may be caused by decreased gluconeogenic enzymes with cortisol deficiency, increased glucose utilization because of a lack of the antagonistic effects of growth hormone on insulin action, or failure to supply endogenous gluconeogenic substrate in the form of alanine and lactate with compensatory breakdown of fat and generation of ketones. Deficiency of these hormones results in reduced gluconeogenic substrate, which resembles the syndrome of ketotic hypoglycemia. Investigation of a child with hypoglycemia, therefore, requires exclusion of ACTH-cortisol or growth hormone deficiency and, if diagnosed, its appropriate replacement with cortisol or growth hormone.

Epinephrine deficiency could theoretically be responsible for hypoglycemia. Urinary excretion of epinephrine has been diminished in some patients with spontaneous or insulin-induced hypoglycemia in whom absence of pallor and tachycardia was also noted, suggesting that failure of catecholamine release, as the result of a defect anywhere along the hypothalamic–autonomic–adrenomedullary axis, might be responsible for the hypoglycemia. This possibility has been challenged, owing to the rarity of hypoglycemia in patients with bilateral adrenalectomy, provided that they receive adequate glucocorticoid replacement, and because diminished epinephrine excretion is found in normal patients with repeated insulin-induced hypoglycemia. Many of the patients described as having hypoglycemia with failure of epinephrine excretion fit the criteria for ketotic hypoglycemia. Also, repetitive hypoglycemia leads to diminished cortisol plus epinephrine responses, as seen most commonly in insulin-treated diabetes mellitus and the syndrome of hypoglycemia unawareness, associated with autonomic failure.

Glucagon deficiency in infants or children may theoretically be associated with hypoglycemia but has never been documented.

Substrate Limited
Ketotic Hypoglycemia
Ketotic hypoglycemia is the most common form of childhood hypoglycemia. This condition usually presents between the ages of 18 mo and 5 yr and commonly remits spontaneously by the age of 8-9 yr. Hypoglycemic episodes typically occur during periods of intercurrent illness when food intake is limited. The classic history is of a child who eats poorly or completely avoids the evening meal, is difficult to arouse from sleep the following morning and hence eats poorly again, and may have a seizure or be comatose by mid-morning. Another common presentation occurs when parents sleep late and the affected child is unable to eat breakfast, thus prolonging the overnight fast.

At the time of documented hypoglycemia, there is associated ketonuria and ketonemia; plasma insulin concentrations are appropriately low, ≤5-10 μU/mL, thus excluding hyperinsulinemia. A ketogenic provocative diet, formerly used as a diagnostic test, is no longer used to establish the diagnosis because fasting alone provokes a hypoglycemic episode with ketonemia and ketonuria within 12-18 hr in susceptible individuals. Normal children of similar age can withstand fasting without hypoglycemia developing during the same period, although
even normal children may acquire these features by 36 hr of fasting.

Children with ketotic hypoglycemia have plasma alanine concentrations that are markedly reduced in the basal state after an overnight fast and decline even further with prolonged fasting. Alanine, produced in muscle, is a major gluconeogenic precursor. Alanine is the only amino acid that is significantly lower in these children, and infusions of alanine (250 mg/kg) produce a rapid rise in plasma glucose without causing significant changes in blood lactate or pyruvate levels, indicating that the entire gluconeogenic pathway from the level of pyruvate is intact, but that there is a deficiency of substrate. Glycogenolytic pathways are also intact because glucagon induces a normal glycemic response in affected children in the fed state. The levels of hormones that counter hypoglycemia are appropriately elevated, and insulin is appropriately low.

The etiology of ketotic hypoglycemia may be a defect in any of the complex steps involved in protein catabolism, oxidative deamination of amino acids, transamination, alanine synthesis, or alanine efflux from muscle. Children with ketotic hypoglycemia are frequently smaller than age-matched controls and often have a history of transient neonatal hypoglycemia. Any decrease in muscle mass may compromise the supply of gluconeogenic substrate at a time when glucose demands per unit of body weight are already relatively high, thus predisposing the patient to the rapid development of hypoglycemia, with ketosis representing the attempt to switch to an alternative fuel supply. Children with ketotic hypoglycemia may represent the low end of the spectrum of children’s capacity to tolerate fasting. Similar relative intolerance to fasting is present in normal children, who cannot maintain blood glucose after 30-36 hr of fasting, compared with the adult’s capacity for prolonged fasting. Although the defect may be present at birth, it may not be evident until the child is stressed by more prolonged periods of calorie restriction. Moreover, the spontaneous remission observed in children at age 8-9 yr might be explained by the increase in muscle bulk with its resultant increase in supply of endogenous substrate and the relative decrease in glucose requirement per unit of body mass with increasing age.

In anticipation of spontaneous resolution of this syndrome, treatment of ketotic hypoglycemia consists of frequent feedings of a high-protein, high-carbohydrate diet. During intercurrent illnesses, parents should be taught to test the child’s urine for the presence of ketones, the appearance of which precedes hypoglycemia by several hours. In the presence of ketonuria, liquids of high carbohydrate content should be offered to the child. If these cannot be tolerated, the child should be treated with intravenous glucose administration in a hospital.

Branched-Chain Ketonuria (Maple Syrup Urine Disease)

See Chapter 85.6.

The hypoglycemic episodes were once attributed to high levels of leucine, but evidence indicates that interference with the production of alanine and its availability as a gluconeogenic substrate during caloric deprivation is responsible for hypoglycemia.

Glycogen Storage Disease

See Chapter 87.1.

Glucose-6-Phosphatase Deficiency (Type I Glycogen Storage Disease)

Affected children usually display a remarkable tolerance to their chronic hypoglycemia; blood glucose values in the range of 20-50 mg/dL are not associated with the classic symptoms of hypoglycemia, possibly reflecting the adaptation of the CNS to ketone bodies and lactate as alternative fuels. Hepatomegaly and poor growth are consistent physical features. Hypoglycemia is associated with acidosis (HCO₃⁻ <18 mEq/L), increased β O-B and lactate; hyperuricemia also is frequent. Management is discussed in detail in Chapter 87.

Amylo-1,6-Glucosidase Deficiency (Debrancher Enzyme Deficiency; Type III Glycogen Storage Disease)

See Chapter 87.

Liver Phosphorylase Deficiency (Type VI Glycogen Storage Disease)

See Chapter 87.

Low hepatic phosphorylase activity may result from a defect in any of the steps of activation; a variety of defects have been described. Hepatomegaly, excessive deposition of glycogen in liver, growth retardation, and occasional symptomatic hypoglycemia occur. A diet high in protein and reduced in carbohydrate usually prevents hypoglycemia.

Glycogen Synthetase Deficiency

See Chapter 87.

The inability to synthesize glycogen is rare. There is hypoglycemia and hyperketonemia after fasting because glycogen reserves are markedly diminished or absent. After feeding, however, hyperglycemia with glucosuria may occur because of the inability to assimilate some of the glucose load into glycogen. During fasting hypoglycemia, levels of the counterregulatory hormones, including catecholamines, are appropriately elevated or normal, and insulin levels are appropriately low. The liver is not enlarged. Protein-rich feedings at frequent intervals result in dramatic clinical improvement, including growth velocity. This condition mimics the syndrome of ketotic hypoglycemia and should be considered in the differential diagnosis of that syndrome.

Disorders of Gluconeogenesis

Fructose-1,6-Diphosphatase Deficiency

See Chapter 87.3.

A deficiency of this enzyme results in a block of gluconeogenesis from all possible precursors below the level of fructose-1,6-diphosphate. Infusion of these gluconeogenic precursors results in lactic acidosis without a rise in glucose; acute hypoglycemia may be provoked by inhibition of glycogenolysis. Glycogenolysis remains intact, and glucagon elicits a normal glycemic response in the fed, but not in the fasted, state. Accordingly, affected individuals have hypoglycemia only during caloric deprivation, as in fasting, or during intercurrent illness. As long as glycogen stores remain normal, hypoglycemia does not develop. In affected families, there may be a history of siblings with known hepaticomegaly who died in infancy with unexplained metabolic acidosis.

Defects in Fatty Acid Oxidation

See Chapter 86.

The important role of fatty acid oxidation in maintaining gluconeogenesis is underscored by examples of congenital or drug-induced defects in fatty acid metabolism that may be associated with fasting hypoglycemia.

Various congenital enzymatic deficiencies causing defective carnitine or fatty acid metabolism occur. A severe and relatively common form of fasting hypoglycemia with hepatomegaly, cardiomyopathy, and hypotonia occurs with long- and medium-chain fatty acid CoA dehydrogenase deficiency. Plasma carnitine levels are low, ketones are not present, but dicarboxylic aciduria is present in urine. Clinically, patients with acyl-CoA dehydrogenase deficiency present with a Reye-like syndrome (see Chapter 361), recurrent episodes of severe fasting hypoglycemic coma, and cardiorespiratory arrest (sudden infant death syndrome-like events). Severe hypoglycemia and metabolic acidosis without ketosis also occur in patients with multiple acyl-CoA dehydrogenase disorders. Hypotonia, seizures, and acrid odor are other clinical clues. Survival depends on whether the defects are severe or mild; diagnosis is established from studies of enzyme activity in liver biopsy tissue or in cultured fibroblasts from affected patients. Tandem mass spectrometry can be employed for blood samples, even those on filter paper, for screening of congenital inborn errors. Molecular diagnosis also is available for most entities. The frequency of this disorder

CoA dehydrogenase disorders. Hypotonia, seizures, and acrid odor are other clinical clues. Survival depends on whether the defects are severe or mild; diagnosis is established from studies of enzyme activity in liver biopsy tissue or in cultured fibroblasts from affected patients. Tandem mass spectrometry can be employed for blood samples, even those on filter paper, for screening of congenital inborn errors. Molecular diagnosis also is available for most entities. The frequency of this disorder
is at least 1 in 10,000-15,000 births. Avoidance of fasting and supplementation with carnitine may be lifesaving in these patients who generally present in infancy.

Interference with fatty acid metabolism also underlies the fasting hypoglycemia associated with Jamaican vomiting sickness, with atracyloside, and with the drug valproate. In Jamaican vomiting sickness, the unripe ackee fruit contains a water-soluble toxin, hypoglycin, which produces vomiting, CNS depression, and severe hypoglycemia. The hypoglyemic activity of hypoglycin derives from its inhibition of gluconeogenesis secondary to its interference with the acyl-CoA and carnitine metabolism essential for the oxidation of long-chain fatty acids. The disease is almost totally confined to Jamaica, where ackee forms a staple of the diet for the poor. The ripe ackee fruit no longer contains this toxin. Atracyloside is a reagent that inhibits oxidative phosphorylation in mitochondria by preventing the translocation of adenine nucleotides, such as ATP, across the mitochondrial membrane. Atracyloside is a pyrophosphoanthenic acid derived from Atractylis gummifera. This plant is found in the Mediterranean basin; ingestion of this “thistle” is associated with hypoglycemia and a syndrome similar to Jamaican vomiting sickness. The anticonvulsant drug valproate is associated with side effects, predominantly in young infants, which include a Reye-like syndrome, low serum carnitine levels, and the potential for fasting hypoglycemia. In all these conditions, hypoglycemia is not associated with ketonuria.

**Acute Alcohol Intoxication**

The liver metabolizes alcohol as a preferred fuel, and generation of reducing equivalents during the oxidation of ethanol alters the reduced form of nicotinamide adenine dinucleotide:nicotinamide adenine dinucleotide ratio, which is essential for certain gluconeogenic steps. As a result, gluconeogenesis is impaired and hypoglycemia may ensue if glycogen stores are depleted by starvation or by preexisting abnormalities in glycogen metabolism. In toddlers who have been unfed for some time, even the consumption of small quantities of alcohol can precipitate these events. The hypoglycemia promptly responds to intravenous glucose, which should always be considered in a child who presents initially with coma or seizure, after taking a blood sample to determine glucose concentration. The possibility of the child’s ingesting alcoholic drinks must also be considered if there was a preceding adult evening party. A careful history allows the diagnosis to be made and may avoid needless and expensive hospitalization and investigation.

**Salicylate Intoxication**

See Chapter 63.

Both hyperglycemia and hypoglycemia occur in children with salicylate intoxication. Accelerated utilization of glucose, resulting from augmentation of insulin secretion by salicylates, and possible interference with gluconeogenesis may contribute to hypoglycemia. Infants are more susceptible than are older children. Monitoring of blood glucose levels with appropriate glucose infusion in the event of hypoglycemia should form part of the therapeutic approach to salicylate intoxication in childhood. Ketosis may occur.

**Phosphoenolpyruvate Carboxykinase Deficiency**

Deficiency of this rate-limiting gluconeogenic enzyme is associated with severe fasting hypoglycemia and variable onset after birth. Hypoglycemia may occur within 24 hr after birth, and defective gluconeogenesis from alanine can be documented in vivo. Liver, kidney, and myocardium demonstrate fatty infiltration, and atrophy of the optic nerve and visual cortex may occur. Hypoglycemia may be profound. Lactate and pyruvate levels in plasma have been normal, but a mild metabolic acidosis may be present. The fatty infiltration of various organs is caused by increased formation of acetyl-CoA, which becomes available for fatty acid synthesis. Diagnosis of this rare entity can be made with certainty only through appropriate enzymatic determinations in liver biopsy material or molecular diagnosis. Avoidance of periods of fasting through frequent feedings rich in carbohydrate should be helpful because glycogen synthesis and breakdown are intact.

**Pyruvate Carboxylase Deficiency**

See Chapter 87.

**Other Enzyme Defects**

- **Galactosemia (Galactose-1-Phosphate Uridyl Transferase Deficiency)**
  See Chapter 87.
- **Fructose Intolerance (Fructose-1-Phosphate Aldolase Deficiency)**
  See Chapter 87.

**Defects in Glucose Transporters**

- **Glut-1 Deficiency**
  Rarely infants with a seizure disorder are found to have low CSF glucose concentrations despite normal plasma glucose. Lactate concentrations in CSF are low, suggesting decreased glycolysis rather than bacterial infection, which causes low CSF glucose with high lactate. The erythrocyte glucose transporter is defective, suggesting a similar defect in the brain glucose transporter responsible for the clinical features. A ketogenic diet reduces the severity of seizures by supplying an alternate source of brain fuel that bypassed the defect in glucose transport.
- **Glut-2 Deficiency**
  Children with hepatomegaly, galactose intolerance, and renal tubular dysfunction (Fanconi-Bickel syndrome) have a deficiency of the GLUT-2 glucose transporter of plasma membranes. In addition to liver and kidney tubules, GLUT-2 is also expressed in pancreatic β cells. Hence, the clinical manifestations reflect impaired glucose release from liver and defective tubular reabsorption of glucose plus phosphaturia and aminoaciduria.

**Systemic Disorders**

Several systemic disorders are associated with hypoglycemia in infants and children. Neonatal sepsis is often associated with hypoglycemia, possibly as a result of diminished caloric intake with impaired gluconeogenesis. Similar mechanisms may apply to the hypoglycemia found in severely malnourished infants or those with severe malabsorption. Hyperviscosity with a central hematocrit of >65% is associated with hypoglycemia in at least 10-15% of affected infants. *Falciparum malaria* is associated with hyperinsulinemia and hypoglycemia. Heart and renal failure are also associated with hypoglycemia, but the mechanism is obscure.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**

Table 92-8 and Figure 92-5 list the pertinent clinical and biochemical findings in the common childhood disorders associated with hypoglycemia. A careful and detailed history is essential in every suspected or documented case of hypoglycemia (see Table 92-7). Specific points to be noted include age at onset, temporal relation to meals or caloric deprivation, and a family history of prior infants known to have had hypoglycemia or of unexplained infant deaths. In the 1st wk of life, the majority of infants have the transient form of neonatal hypoglycemia either as a result of prematurity/intrauterine growth restriction or by virtue of being born to diabetic mothers. The absence of a history of maternal diabetes, but the presence of macrosomia and the characteristic large plethoric appearance of an “infant of a diabetic mother” should arouse the possibility of hyperinsulinemic hypoglycemia of infancy, probably resulting from a K<sub>ATP</sub> channel defect that is familial (autosomal recessive) or sporadic; decreased β OH butyrate, low FFAs, and plasma insulin concentrations >5-10 μU/mL in the presence of documented hypoglycemia confirm this diagnosis. The presence of
hepatomegaly should arouse suspicion of an enzyme deficiency such as glucose-6-phosphate in glycogen storage disease-1 or other glycerogen storage diseases; if a non–glucose-reducing sugar is present in the urine (e.g., Clinitest positive but Clinistix negative), galactosemia is most likely. In males, the presence of a microphallus suggests the possibility of hypopituitarism, which also may be associated with cholestatic jaundice in both sexes; evidence of a midline facial defect such as cleft palate also suggests possible hypopituitarism as the cause of hypoglycemia via deficiency in growth hormone and/or cortisol. A high index of suspicion and awareness of hypoglycemia as the cause for unusual behavior of any “sick” newborn should prompt a bedside glucose determination. However, because glucose meters have an accuracy of only ±20%, any blood glucose value <60 mg/dL must be confirmed by a formal laboratory measurement that is performed without delay on a blood sample preserved in a tube that prevents glycolysis, which can cause spurious low values.

Past the newborn period, clues to the cause of persistent or recurrent hypoglycemia may be obtained through a careful history, physical examination, and initial laboratory findings. The temporal relation of the hypoglycemia to food intake may suggest that the defect is one of gluconeogenesis, if symptoms occur 6 hr or more after meals. If hypoglycemia occurs shortly after meals, hyperinsulinism should be suspected and confirmed or excluded via measurement of β OH butyrate, insulin, and FFA in a sample in which blood glucose is <50 mg/dL. The autosomal dominant forms of hyperinsulinemic hypoglycemia need to be considered, with measurement of glucose, insulin, and ammonia, and careful history for other affected family members of any age. Measurement of IGFBP-1 may be useful; it is low in states of hyperinsulinism and high in other forms of hypoglycemia. The presence of hepatomegaly suggests one of the enzyme deficiencies in glycogen breakdown or in gluconeogenesis, as outlined in Table 92-8. The absence of ketonemia or ketonuria at the time of initial presentation strongly suggests hyperinsulinism or a defect in fatty acid oxidation. In most other causes of hypoglycemia, with the exception of galactosemia and fructose intolerance, ketonemia and ketonuria are present at the time of fasting hypoglycemia. At the time of the hypoglycemia, serum should be obtained for determination of substrates especially β OH butyrate, lactate and FFA as well as hormones especially insulin, cortisol, ACTH, and growth hormone, followed by repeated measurement after an intramuscular or intravenous injection of glucagon, as outlined in Table 92-7. Table 92-8 summarizes the interpretation of the findings. Hypoglycemia with ketonuria in children between ages 18 mo and 5 yr is most likely to be ketotic hypoglycemia, especially if hepatomegaly is absent. The ingestion of a toxin, including alcohol or salicylate, can usually be excluded rapidly by the history. Inadvertent or deliberate drug ingestion and errors in dispensing medicines should also be considered. Munchausen by proxy should be considered when parents or other caregivers have access to insulin or insulin secretagogues—high insulin concentrations in the sample with low concentrations of C-peptide confirm exogenous insulin administra-

### Treatment

The prevention of hypoglycemia and its resultant effects on CNS development are critically important in the newborn period. For neonates with hyperinsulinism not associated with maternal diabetes, subtotal or focal pancreatectomy may be needed, unless hypoglycemia can be readily controlled with long-term diazoxide, somatostatin analogs (e.g., octreotide), or sirolimus.

**Treatment of acute symptomatic** Neonatal or infant hypoglycemia includes intravenous administration of 2 mL/kg of 10% dextrose in water (D10W), followed by a continuous infusion of glucose at 6-8 mg/kg/min, adjusting the rate to maintain blood glucose levels in the normal range. If hypoglycemic seizures are present, some recommend a 4 mL/kg bolus of D10W.

**Treatment of asymptomatic** hyperglycemia in at risk infants usually includes enteral feedings rather than parenteral glucose. If symptoms develop or the hypoglycemia persists despite enteral feedings, intravenous glucose is indicated. Dextrose gel (40% at 400 mg/kg)
administered into the mouth may be an alternative to enteral feedings if breast milk or if formula is not available.

The management of persistent neonatal or infantile hypoglycemia includes increasing the rate of intravenous glucose infusion to 10-15 mg/kg/min or more, if needed. This may require a central venous or umbilical venous catheter to administer a hypertonic 15-25% glucose solution. If hyperinsulinism is present, it should be medically managed initially with diazoxide and then somatostatin analogs. If hypoglycemia is unresponsive to intravenous glucose plus diazoxide (maximal doses up to 15-20 mg/kg/day) and somatostatin analogs, surgery via partial or near-total pancreatectomy should be considered. Such surgery should be performed in centers with the requisite facilities, and trained staff experienced in the procedures. If possible, surgery should be preceded by [18F]-DOPA scanning to localize a lesion which can then provide guidance to the surgeon for curative resection before the operation is undertaken.

Oral diazoxide, 5-15 mg/kg/24 hr given in divided doses twice daily, may reverse hyperinsulinemic hypoglycemia but may also produce hirsutism, edema, nausea, hyperuricemia, electrolyte disturbances, advanced bone age, immunoglobulin G deficiency, and, rarely, hypotension with prolonged use. The long-acting somatostatin analog octreotide may be helpful in controlling hyperinsulinism causing hypoglycemia in patients with islet cell disorders, including genetic mutations in KATP channel and islet cell adenoma. Glucagon given by continuous IV infusion at 5 µg/kg/hr together with octreotide administered subcutaneously every 6-12 hr in doses of 20-50 µg/kg/day in neonates and young infants may maintain blood glucose, but generally these agents are used as a temporizing measure before surgery for partial or more complete pancreatectomy. Potential but unusual complications of octreotide include poor growth because of inhibition of growth hormone release, pain at the injection site, vomiting, diarrhea, and hepatic dysfunction (hepatitis, cholelithiasis), and necrotizing enterocolitis; tachyphylaxis to the drug’s effects is more common. It may be particularly useful for the treatment of refractory hypoglycemia despite subtotal pancreatectomy. Total pancreatectomy is not optimal therapy, owing to the risks of surgery, permanent diabetes mellitus, and exocrine pancreatic insufficiency. Continued prolonged medical therapy without pancreatic resection if hypoglycemia is controllable is worthwhile, because over time some children have a spontaneous resolution of the hyperinsulinism-induced hypoglycemia. This should be balanced against the risk of hypoglycemia-induced CNS injury and the toxicity of drugs.

PROGNOSIS

The prognosis is good in asymptomatic neonates with hypoglycemia of short duration. Hypoglycemia recurs in 10-15% of infants after adequate treatment. Recurrence is more common if intravenous fluids are extravasated or discontinued too rapidly before oral feedings are well tolerated. Children who had transient neonatal hypoglycemia have an increased incidence of ketotic hypoglycemia later in life. The prognosis for normal intellectual function must be guarded because prolonged, recurrent, and severe symptomatic hypoglycemia is associated with neurologic sequelae. Symptomatic infants with hypoglycemia, particularly low-birthweight infants, those with persistent hyperinsulinemic hypoglycemia, and severely hypoglycemic infants born to poorly controlled diabetic mothers, have a poorer prognosis for subsequent normal intellectual development than asymptomatic infants do.

Bibliography is available at Expert Consult.
Bibliography
The Fetus and the Neonatal Infant

Chapter 93
Overview of Mortality and Morbidity
Waldemar A. Carlo

The risk for mortality in fetuses and neonates is very high around the time of birth. The perinatal period is most often defined as the period from the 28th wk of gestation through the 7th day after birth. The neonatal period is defined as the 1st 28 days after birth and may be further subdivided into the very early (birth to <24 hr), early (birth to <7 days), and late neonatal periods (7 days to <28 days). Infancy is defined as the 1st yr after birth.

Perinatal mortality is influenced by prenatal, maternal, and fetal conditions and by circumstances surrounding delivery. Perinatal deaths are associated with intrauterine growth restriction (IUGR); conditions that predispose the fetus to asphyxia, such as placental insufficiency; severe congenital malformations; and overwhelming early-onset neonatal infections (Table 93-1). The major causes of neonatal mortality are prematurity/low birthweight (LBW) and congenital anomalies (Fig. 93-1). Mortality is highest during the 1st 24 hr after birth. Neonatal mortality (4.04/1,000 in 2011) accounts for about two-thirds of all infant deaths (deaths before 1 yr of age). Neonatal and postneonatal mortality rates in the United States have declined slightly in the last decade (Fig. 93-2). Factors related to the decline in mortality include improved obstetric and neonatal intensive care management with a significant reduction in birthweight-specific neonatal mortality (Fig. 93-3). Further reduction in neonatal mortality will depend on prevention of preterm delivery and LBW, prenatal diagnosis and early management of congenital anomalies, and effective diagnosis and treatment of diseases that result from adverse factors during pregnancy, labor, and/or delivery (see Table 93-1). In the United States each year, approximately 6 million pregnancies, 4 million live births, 19,000 neonatal deaths, and 28,000 infant deaths occur. Approximately 10% of births are to teenage women between the ages of 15 and 19 yr, a proportion that has been decreasing for approximately 50 yr (Fig. 93-4). Births to girls 10-14 yr of age, very young mothers who are at great social and medical risk, declined substantially over this period.

Infant mortality rates (deaths occurring from birth to 12 mo per 1,000 live births) vary by country; in 2010, rates were lowest in Hong Kong (1.7/1,000 births), moderate in the United States (6.1/1,000), and highest in developing, resource-poor countries (30-150/1,000). Medical, socioeconomic, and cultural factors influence perinatal and neonatal mortality. Preventive variables such as health education, prenatal care, nutrition, social support, risk identification, and obstetric care can effectively reduce perinatal, neonatal, and infant mortality. A number of reasons can explain in part the relatively higher infant mortality in the United States than in other countries. There is evidence of differential reporting of live births versus fetal deaths or stillbirths among countries. Many countries do not report as live births those of infants as mature as up to 27 wk if they die early after birth. The reporting of vital events in the United States is more complete than in many countries, including developed countries. This situation in part explains the larger proportion of LBW/preterm infants in the United States than in other countries. Increases in recorded preterm live births, especially of the most immature infants (<500 g body weight) in the United States, result in increases in both neonatal and infant mortality rates.

Nonetheless, continuing healthcare disparities in part account for the higher infant mortality rate in the United States. Infants of African-American women continue to have a high infant mortality rate (12.76/1,000), which is more than twice the rates of infants of white (5.52/1,000) and Hispanic mothers (4.76/1,000 Central and South American vs. 7.29/1,000 Puerto Rican).

In the United States, approximately 50% of infant deaths in 2011 were a consequence of 4 conditions (classified according to the International Classification of Diseases, 10th revision): congenital malformations (20.1%), disorders relating to prematurity and unspecified LBW (16.9%), sudden infant death syndrome (8.2%), and newborns affected by maternal complications of pregnancy (6.3%). LBW (as a result of preterm delivery and/or IUGR) is a major determinant of both neonatal and infant mortality rates and, together with congenital anomalies (cardiac, central nervous system, respiratory), contributes significantly to childhood morbidity. In developing countries, LBW/prematurity, birth asphyxia, and infections are the major causes of infant deaths.

The LBW rate (infants weighing <2,500 g at birth each year) in the United States increased from 6.6% to 8.2% between 1981 and 2008, whereas the very-low birthweight (VLBW) rate (infants weighing ≤1,500 g at birth) increased from 1.1% to 1.46% of all births. In the past decade, LBW has increased among white infants, mainly because of a rise in the number of multiple births (often associated with assisted reproduction). Nonetheless, LBW and VLBW rates remain highest among black infants. Reasons for the racial disparity in LBW remain unclear. Despite advances in prenatal and obstetric care, racial disparity in birthweight persists, thus suggesting the need for novel prevention programs. Furthermore, although preterm LBW survival is better among black neonates, overall neonatal and infant mortality rates remain highest among blacks (Fig. 93-5), even for infants born to extremely low-risk mothers (married, age 20-34 yr, ≤21 yr of education, adequate prenatal care, no medical risk factors, no alcohol or tobacco use during pregnancy). A reduction in the racial disparity in mortality is an important public health issue reflected in Healthy People 2020, the U.S. national health objectives for the year 2020.

LBW is caused by preterm birth, IUGR, or both. The predominant cause of LBW in the United States is preterm birth, whereas in developing countries, the cause is more often IUGR. Although IUGR does not appear to further increase the risk of mortality in preterm infants, both morbidity and mortality are increased in term growth-restricted infants. VLBW infants are most often premature (<37 wk of gestation), although IUGR may also complicate their early delivery. Even though VLBW occurs in only 1-2% of all infants in the United States, their births represent a large proportion of the neonatal and infant mortality, as well as of infants with both short- and long-term complications, including neurodevelopmental handicaps. The etiology of preterm birth is complex, multifactorial, and not completely understood. Causes include maternal diseases such as severe preeclampsia requiring elective delivery, premature rupture of membranes, uterine abnormalities, placental bleeding (abruptio, previa), multiple-fetus gestation, drug misuse, maternal chronic illnesses, fetal distress, and infection. A complex interaction can be noted among infection, inflammation, and both preterm premature rupture of membranes and preterm birth. Infectious antecedents include maternal urinary tract infection, chorioamnionitis, bacterial vaginosis, and upper and lower genital tract infection with a variety of agents (Chlamydia trachomatis, Ureaplasma urealyticum, Mycoplasma hominis, Gardnerella vaginalis, and group B streptococcus). Preconceptional dietary folate supplementation may effectively reduce the rate of spontaneous...
**Figure 93-1** Infant mortality rates for the 5 leading causes of infant death in 2011: United States, 2005 and 2011. *(From CDC/NCHS, National Vital Statistics, mortality data set. NCHS Data Brief, No. 120, April 2013.)*

**Figure 93-2** Infant, neonatal, and postneonatal mortality rates: United States, 2000 and 2005-2011. *(From CDC/NCHS, National Vital Statistics, mortality data set. NCHS Data Brief, No. 120, April 2013.)*

**Figure 93-3** Birthweight-specific neonatal mortality—United States, 1950, 1985, and 2008. *(From Centers for Disease Control and Prevention: Grand rounds: public health approaches to reducing U.S. infant mortality. MMWR Morb Mortal Wkly Rep 62(31):425–428, 2013, Fig. 3, p. 627.)*
preterm birth. In many cases, the cause of preterm delivery is unknown. The number of late preterm births (34-36 wk) has increased owing in part to elective deliveries; late preterm neonates are also at increased risk for morbidity and mortality. If possible, elective delivery should be delayed until ≥39 wk.

Although 99% of births occur in hospitals, only 80-85% of pregnant women receive ideal prenatal care in the 1st trimester. Many women who receive inadequate prenatal care are at risk for perinatal complications. Barriers to prenatal care include lack or insufficiency of money or insurance to pay for care; poor coordination of services, including language and cultural issues; and inadequate effective education about the importance of prenatal care. Successful and adequate provision of high-quality prenatal care requires competent healthcare professionals and coordination of services among physicians’ offices, clinics, community hospitals, specially regionalized programs for high-risk mothers and infants, and tertiary care centers. Regional perinatal programs should provide continuing education and consultation in both the community and the referral center and transportation for pregnant women and newborn infants to appropriate hospitals; they should also include a regional hospital with facilities, equipment, and personnel for obstetric and neonatal intensive care (Table 93-2).

Fetal deaths slightly exceed neonatal deaths in their contribution to perinatal mortality. The fetal mortality rate in the United States has been declining steadily during the last 2 decades and decreased to 6.2/1000 in 2004. Obstetricians and maternal–fetal medicine subspecialists have a central role in reducing perinatal mortality and
morbidity. The overall decrease in fetal death has been from a reduction in late fetal deaths (≥28 wk). Intrapartum fetal deaths have declined more than antepartum fetal deaths, reflecting improvements in care during labor and delivery. It is important to emphasize the ability to predict the maturity and functional reserve of a fetus both before and during labor so that fetuses and infants at greatest risk can be identified as early as possible. The obstetrician and pediatrician must interact effectively to anticipate perinatal problems and take prompt preventive and therapeutic measures.

Causes of intrauterine fetal demise include obstetric conditions (preeclampsia, others), placental and umbilical cord abnormalities, genetic and syndromic disorders, intrauterine infections, fetal growth restriction, and preexisting maternal diseases. In approximately 40% of intrauterine fetal demise, there is no identifiable etiology.

Postneonatal mortality refers to deaths between 28 days and 1 yr of life. Historically, these infant deaths were a result of causes outside the neonatal period, such as sudden infant death syndrome, infections (respiratory, enteric), and trauma. With the advent of modern neonatal care, many VLBW and preterm infants who would have died in the 1st mo of life now survive the neonatal period only to succumb to the sequelae listed in Table 93-3. This delayed neonatal mortality is an important contributor to postneonatal mortality and explains its lack of decline during the last years.

Late preterm infants are at risk for hypothermia, hypoglycemia, respiratory distress, apnea, jaundice, feeding difficulties, dehydration, and suspected sepsis. They are also at risk of having rehospitalizations. Even term infants born at 37 and 38 wk by cesarean section are at increased risk for respiratory distress syndrome, transient tachypnea of the newborn, suspected sepsis, hypoglycemia, need for ventilatory support, and admission to the neonatal intensive care unit (Table 93-4).

For the most immature infants at the limit of viability (22-25 wk gestation), decision making about care is a complex process that involves the physician, other health professionals, and the family. The challenge for all premature infants is not only to improve survival, but also to reduce short-term complications and improve long-term neurodevelopmental outcome. Adverse neurodevelopmental sequelae include cerebral palsy, seizures, hydrocephalus requiring a shunt, blindness, deafness, and cognitive impairment. The risk of an adverse outcome increases with decreasing gestational age at birth. Higher birthweight, female gender, singleton birth, and antenatal steroids reduce the risk of neurodevelopment impairment or death. Early morbidity and prognostic variables that contribute to adverse neurodevelopmental outcomes include intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis requiring extensive bowel resection, neonatal infection, and bronchopulmonary dysplasia. Many studies have documented the impact of adverse social and family risk factors on poor outcome.

### Table 93-1 Major Causes of Perinatal and Neonatal Mortality

<table>
<thead>
<tr>
<th>FETAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placental insufficiency</td>
</tr>
<tr>
<td>Intrauterine infection</td>
</tr>
<tr>
<td>Severe congenital malformations (anomalies)</td>
</tr>
<tr>
<td>Umbilical cord accident</td>
</tr>
<tr>
<td>Abruptio placenta</td>
</tr>
<tr>
<td>Hydrops fetalis</td>
</tr>
<tr>
<td>PRETERM</td>
</tr>
<tr>
<td>Severe immaturity</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
</tr>
<tr>
<td>Congenital anomalies</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia (BPD)</td>
</tr>
<tr>
<td>FULL TERM</td>
</tr>
<tr>
<td>Congenital anomalies</td>
</tr>
<tr>
<td>Birth asphyxia</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Meconium aspiration pneumonia</td>
</tr>
<tr>
<td>Persistent pulmonary hypertension (PPHN)</td>
</tr>
</tbody>
</table>

### Table 93-2 Levels of In-Hospital Perinatal Care

<table>
<thead>
<tr>
<th>MATERNAL</th>
<th>NEONATE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BASIC</strong></td>
<td><strong>Resuscitation</strong></td>
</tr>
<tr>
<td>Monitor and care for low-risk patients</td>
<td>Stabilization</td>
</tr>
<tr>
<td>Triage for high risk for transfer</td>
<td>Well neonatal care</td>
</tr>
<tr>
<td>Detection and care of unanticipated labor problems</td>
<td>Nursery care</td>
</tr>
<tr>
<td>Emergency cesarean delivery within 30 min</td>
<td>Visitation</td>
</tr>
<tr>
<td>Blood bank, anesthesia, radiology, ultrasound, and laboratory support</td>
<td>General pediatrician staff (capable of neonatal resuscitation)</td>
</tr>
<tr>
<td>Care of postpartum problems</td>
<td><strong>SPECIAL CARE</strong></td>
</tr>
<tr>
<td>Obstetrician, nurse, midwife staff</td>
<td>Basic services plus:</td>
</tr>
<tr>
<td><strong>SPECIAL CARE</strong></td>
<td>Care of high-risk neonate with short-term problems</td>
</tr>
<tr>
<td>Basic services plus:</td>
<td>Stabilization before transfer (&lt;1,500 g, &lt;32 wk, critically ill)</td>
</tr>
<tr>
<td>Care of high-risk pregnancies</td>
<td>Accept convalescing back (reverse) transfers</td>
</tr>
<tr>
<td>Triage, transfer of high-risk pregnancies (&lt;32 wk, intrapartum growth retardation, preeclampsia, severe maternal medical illness)</td>
<td><strong>SUBSPECIALTY CARE</strong></td>
</tr>
<tr>
<td><strong>SUBSPECIALTY CARE</strong></td>
<td>Basic plus specialty care plus:</td>
</tr>
<tr>
<td>Basic plus specialty care plus:</td>
<td>Experienced neonatologist (24-hr coverage)</td>
</tr>
<tr>
<td>Experienced perinatologist (24-hr coverage)</td>
<td>Inborn plus transferred patients</td>
</tr>
<tr>
<td>Evaluation of high-risk therapies</td>
<td>Evaluation of high-risk therapies</td>
</tr>
<tr>
<td>Care for severe maternal medical or obstetric illnesses</td>
<td>All pediatric medical, radiologic, and surgical subspecialties</td>
</tr>
<tr>
<td>High-risk fetal care (Rh disease, nonimmune hydrops, life-threatening anomalies)</td>
<td>Neonatal intensive care unit with operating room capabilities</td>
</tr>
<tr>
<td>Outcomes research</td>
<td>High-risk follow-up</td>
</tr>
<tr>
<td>Community education</td>
<td>Outcomes research</td>
</tr>
<tr>
<td><strong>Community education</strong></td>
<td><strong>Community education</strong></td>
</tr>
</tbody>
</table>

Table 93-3  Morbidities and Sequelae of Perinatal and Neonatal Illness

<table>
<thead>
<tr>
<th>MORBIDITIES</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>CENTRAL NERVOUS SYSTEM</td>
<td>Hypoxic–ischemic encephalopathy, periventricular leukomalacia, undetermined antenatal factors</td>
</tr>
<tr>
<td>Spastic diplegic–quadriplegic cerebral palsy</td>
<td>Bilirubin encephalopathy (kernicterus)</td>
</tr>
<tr>
<td>Choreothetotic cerebral palsy</td>
<td>Hypoxic-ischemic encephalopathy, intrauterine infection (rubella, CMV)</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>Intraventricular hemorrhage, meningitis</td>
</tr>
<tr>
<td>Communicating hydrocephalus</td>
<td>Hypoxic-ischemic encephalopathy, hypoglycemia</td>
</tr>
<tr>
<td>Seizures</td>
<td>Congenital infections (rubella, CMV, HIV, toxoplasmosis)</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>Immaturity, hypoxia, hypoglycemia, cerebral palsy, intraventricular hemorrhage, low socioeconomic status</td>
</tr>
<tr>
<td>Educational failure and/or mental retardation</td>
<td></td>
</tr>
</tbody>
</table>

| SENSATION—PERIPHERAL NERVES | |
| Reduced visual acuity (blindness) | Retinopathy of prematurity |
| Strabismus | Undetermined, prematurity |
| Hearing impairment (deafness) | Drug toxicity (furosemide, aminoglycosides), bilirubin encephalopathy, hypoxia ± hyperventilation |
| Poor speech | Immaturity, chronic illness, hypoxia, prolonged endotracheal intubation, hearing deficit |
| Paralysis—paresis | Birth trauma—brachial plexus, phrenic nerve, spinal cord |

| RESPIRATORY | |
| BPD | Oxygen toxicity, barotrauma |
| Subglottic stenosis | Endotracheal tube injury |
| Sudden infant death syndrome | Prematurity, BPD, infant of illicit drug user |
| Choanal stenosis, nasal septum destruction | Nasotracheal intubation |
| | Growth failure |

| CARDIOVASCULAR | |
| Cyanosis | Precorrective palliative care of congenital cyanotic heart disease, cor pulmonale from BPD, reactive airway |
| Heart failure | Precorrective palliative care of complex congenital heart disease, BPD, ventricular septal defect |

| GASTROINTESTINAL | |
| Short-gut syndrome | Necrotizing enterocolitis, gastrochisis, malrotation-volvulus, cystic fibrosis, intestinal atresia |
| Cholestatic liver disease (cirrhosis, hepatic failure) | Hyperalimentation toxicity, sepsis, short-gut syndrome |
| Failure to thrive | Short-gut syndrome, cholestasis, BPD, cerebral palsy, severe congenital heart disease |
| Inguinal hernia | Unknown |

| MISCELLANEOUS | |
| Cutaneous scars | Chest tube or intravenous catheter placement, hyperalimentation, subcutaneous infiltration, fetal puncture, intrauterine varicella, cutis aplasia |
| Absence of radial artery pulse | Frequent arterial puncture |
| Hypertension | Renal thrombi, repair of coarctation of aorta |

BPD, bronchopulmonary dysplasia; CMV, cytomegalovirus.

Table 93-4  Incidence of Adverse Outcome According to Completed Week of Gestation at Delivery for Infants Born by Caesarean Section

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>WK 37 (N = 934)</th>
<th>WK 38 (N = 3909)</th>
<th>WK 39 (N = 6512)</th>
<th>WK 40 (N = 1385)</th>
<th>WK 41 (N = 1385)</th>
<th>WK 42 (N = 113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory distress syndrome</td>
<td>3.7</td>
<td>1.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Transient tachypnea of the newborn</td>
<td>4.8</td>
<td>3.9</td>
<td>2.7</td>
<td>2.5</td>
<td>4.8</td>
<td>6.2</td>
</tr>
<tr>
<td>Admission to the neonatal intensive care unit</td>
<td>12.8</td>
<td>8.1</td>
<td>5.9</td>
<td>4.8</td>
<td>7.9</td>
<td>14.2</td>
</tr>
<tr>
<td>Suspected sepsis</td>
<td>6.6</td>
<td>3.9</td>
<td>2.4</td>
<td>2.6</td>
<td>3.6</td>
<td>10.6</td>
</tr>
<tr>
<td>Treated hypoglycemia</td>
<td>2.4</td>
<td>0.9</td>
<td>0.7</td>
<td>0.8</td>
<td>1.6</td>
<td>1.8</td>
</tr>
<tr>
<td>Ventilation</td>
<td>1.9</td>
<td>0.9</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
</tr>
</tbody>
</table>


High-risk infants must be monitored after discharge so that neurodevelopmental impairment is detected as early as possible and to ensure that children and families receive any interventions indicated and adequate support to optimize long-term outcome. At school age, former VLBW and preterm infants have poorer physical growth, cognitive function, and school performance. Although disadvantages may persist into adulthood, data now suggest that there may be cognitive improvement throughout childhood.

Bibliography is available at Expert Consult.
Chapter 93  Overview of Mortality and Morbidity  793.e1

Bibliography
The neonatal period is a highly vulnerable time for infants as they are completing many of the physiologic adjustments required for extrauterine existence. The high neonatal morbidity and mortality rates attest to the fragility of life during this period; of all deaths occurring in the 1st yr of life in the United States, two-thirds are in the neonatal period. The annual rate of deaths during the 1st yr is unequaled by the rate in any other period of life until the 7th decade.

94.1 History in Neonatal Pediatrics

Waldemar A. Carlo

The perinatal history should include the following information:
- Demographic and social data: socioeconomic status, age, race
- Past medical illnesses in the mother and family, including previous siblings: cardiopulmonary disorders, infectious diseases, genetic disorders, anemia, jaundice, diabetes mellitus
- Previous maternal reproductive problems: stillbirth, prematurity, blood group sensitization
- Events occurring in the present pregnancy: preterm labor, fetal assessments, vaginal bleeding, medications, acute illness, duration of rupture of membranes
- Description of the labor (duration, fetal presentation, fetal distress, fever) and delivery (cesarean section, anesthesia or sedation, use of forceps, Apgar scores, need for resuscitation)

94.2 Physical Examination of the Newborn Infant

Waldemar A. Carlo

Many physical and behavioral characteristics of a normal newborn infant are described in Chapters 9 and 590.

The initial examination of a newborn infant should be performed as soon as possible after delivery. Temperature, pulse, respiratory rate, color, signs of respiratory distress, tone, activity, and level of consciousness of infants should be monitored frequently until stabilization. For high-risk deliveries, this examination should take place in the delivery room and should focus on congenital anomalies, matura
tion and growth, and pathophysiologic problems that may interfere with normal cardiopulmonary and metabolic adaptation to extrauterine life. Congenital anomalies of varying degrees of severity may be present in 3-5% of infants. After a stable delivery room course, a second and more detailed examination should be performed within 24 hr of birth. If an infant remains in the hospital longer than 48 hr, a discharge examination should be performed within 24 hr of discharge. For a healthy infant, the mother should be present during this examination; even minor, seemingly insignificant anatomic variations may worry the parents and should be explained. The explanation must be careful and skillful so that otherwise unworried parents are not unduly alarmed. Infants should not be discharged from the hospital without a final examination because certain abnormalities, particularly cyanosis and heart murmurs, often appear or disappear in the immediate neonatal period; in addition, evidence of disease that has just been acquired may be noted. The pulse (normal: 120-160 beats/ min), respiratory rate (normal: 30-60 breaths/min), temperature, weight, length, head circumference, and dimensions of any visible or palpable structural abnormality should be assessed. Blood pressure is determined if a neonate appears ill or has a heart murmur. Pulse oximetry should be performed to screen for critical congenital heart disease and is part of the routine screening for newborn infants. An oxygen saturation ≥95% test after 24 hr after birth in otherwise healthy appearing term infants has >99% sensitivity and specificity to rule out critical congenital heart disease. Neonates with oxygen saturations <95% should be referred for evaluation and possible echocardiogram (see Chapter 425).

Examining a newborn requires patience, gentleness, and procedural flexibility. Thus, if the infant is quiet and relaxed at the beginning of the examination, palpation of the abdomen or auscultation of the heart should be performed first, before other, more disturbing manipulations are attempted.

**GENERAL APPEARANCE**

Physical activity may be absent during normal sleep, or it may be decreased by the effects of illness or drugs; an infant may be either lying with the extremities motionless, to conserve energy for the effort of difficult breathing, or vigorously crying, with accompanying activity of the arms and legs. Both active and passive muscle tone and any unusual posture should be noted. Coarse, tremulous movements with ankle or jaw myoclonus are more common and less significant in newborn infants than at any other age. Such movements tend to occur when an infant is active, whereas convulsive twitching usually occurs in a quiet state. Edema may produce a superficial appearance of good nutrition. Pitting after applied pressure may or may not be noted, but the skin of the fingers and toes lacks the normal fine wrinkles when filled with fluid. Edema of the eyelids commonly results from irritation caused by the administration of silver nitrate. Generalized edema may occur with prematurity, hyponatremia secondary to severe erythroblastosis fetalis, nonimmune hydrops, congenital nephrosis, Hurler syndrome, and from unknown causes. Localized edema suggests a congenital malformation of the lymphatic system; when confined to one or more extremities of a female infant, it may be the initial sign of Turner syndrome (see Chapters 81 and 586).

**SKIN**

Vasomotor instability and peripheral circulatory sluggishness are revealed by deep redness or purple lividity in a crying infant, whose color may darken profoundly with closure of the glottis preceding a vigorous cry, and by harmless cyanosis (acrocyanosis) of the hands and feet, especially when they are cool. Mottling, another example of general circulatory instability, may be associated with serious illness or related to a transient fluctuation in skin temperature. An extraordinary division of the body from the forehead to the pubis into red and pale halves is known as harlequin color change, a transient and harmless condition. Significant cyanosis may be masked by the pallor of circulatory failure or anemia; alternatively, the relatively high hemoglobin content of the 1st few days and the thin skin may combine to produce an appearance of cyanosis at a higher PaO₂ (partial pressure arterial oxygen) than in older children. Localized cyanosis is differentiated from ecchymosis by the momentary blanching pallor (with cyanosis) that occurs after pressure. The same maneuver also helps in demonstrating icterus. Pallor may be caused by anemia, asphyxia, shock, or edema. Early recognition of anemia may lead to a diagnosis of fetomaternal blood transfusion, erythroblastosis fetalis, subcapsular hematoma of the liver or spleen, subdural hemorrhage, or fetal–maternal or twin–twin transfusion. Without being anemic, postmature infants tend to have paler and thicker skin than term or premature infants. The ruddy appearance of plethora is seen with prematurity, hypoproteinemia secondary to severe erythroblastosis fetalis, nonimmune hydrops, congenital nephrosis, Hurler syndrome, and from unknown causes. Localized edema suggests a congenital malformation of the lymphatic system; when confined to one or more extremities of a female infant, it may be the initial sign of Turner syndrome (see Chapters 81 and 586).
hemangiomas are deeper, blue masses that, if large, may trap platelets and produce disseminated intravascular coagulation or interfere with local organ function. Scattered petechiae may be seen on the presenting part (usually the scalp or face) after a difficult delivery. Slate-blue, well-demarcated areas of pigmentation called Mongolian spots are seen over the buttocks, back, and sometimes other parts of the body in more than 50% of black, Native American, and Asian infants, and occasionally in white infants. These benign patches have no known anthropologic significance despite their name; they tend to disappear within the 1st year. The vernix, skin, and especially the cord may be stained brownish yellow if the amniotic fluid has been colored by the passage of meconium during or before birth.

The skin of premature infants is thin and delicate and tends to be deep red; in extremely premature infants, the skin appears almost gelatinous and translucent. Fine, soft, immature hair called lanugo frequently covers the scalp and may also cover the face of premature infants. Lanugo has usually been lost or replaced by vellus hair in term infants. Tufts of hair over the lumbosacral spine suggest an underlying abnormality, such as occult spina bifida, a sinus tract, or a tumor. The nails are rudimentary in very premature infants, but they may protrude beyond the fingertips in infants born past term. Postterm infants may have a peeling, parchment-like skin (Fig. 94-1), a severe degree of which may mimic ichthyosis congenita (see Chapter 658).

In many neonates, small, white papules on an erythematous base develop 1-3 days after birth. This benign rash, erythema toxicum, persists for as long as 1 wk, contains eosinophils, and is usually distributed on the face, trunk, and extremities (see Chapter 647). Pustular melanosis, a benign lesion seen predominantly in black neonates, contains neutrophils and is present at birth as a vesiculopustular eruption around the chin, neck, back, extremities, and palms or soles; it lasts 2-3 days. Both lesions need to be distinguished from more dangerous vesicular eruptions such as herpes simplex (see Chapter 252) and staphylococcal disease of the skin (see Chapter 181.1).

Amniotic bands may disrupt the skin, extremities (amputation, ring constriction, syndactyly), face (clefts), or trunk (abdominal or thoracic wall defects). Their cause is uncertain but may be related to amniotic membrane rupture or vascular compromise with fibrous band formation. Excessive skin fragility and extensibility with joint hypermobility suggest Ehlers-Danlos syndrome, Marfan syndrome, congenital contractual arachnodactyly, and other disorders of collagen synthesis.

SKULL

The head circumference of all infants should be plotted on a growth chart to rule out microcephalus and megalencephaly. The skull may be molded, particularly if the infant is the first-born and if the head has been engaged in the pelvic canal for a considerable time. The parietal bones tend to override the occipital and frontal bones. The head of an infant born by cesarean section or from a breech presentation is characterized by its roundness. The suture lines and the size and fullness of the anterior and posterior fontanels should be determined digitally by palpation. Premature fusion of sutures (cranial synostosis) is identified as a hard nonmovable ridge over the suture and an abnormally shaped skull. Great variation in the size of the fontanels exists at birth; if small, the anterior fontanel usually tends to enlarge during the first few mo after birth. The persistence of excessively large anterior (normal: 20 ± 10 mm) and posterior fontanels has been associated with several disorders (Table 94-1). Persistently small fontanels suggest microcephaly, craniosynostosis, congenital hyperthyroidism, or wormian bones; presence of a third fontanel suggests trisomy 21, but is seen in preterm infants. Soft areas (craniotabes) are occasionally found in the parietal bones at the vertex near the sagittal suture; they are more common in preterm infants and in infants who have been exposed to uterine compression. Although such soft areas are usually insignificant, their possible pathologic cause should be investigated if they persist. Soft areas in the occipital region suggest the irregular calcification and wormian bone formation associated with osteogenesis imperfecta, cleidocranial dysostosis, lacunar skull, cleftsin, and, occasionally, Down syndrome. Transillumination of an abnormal skull in a dark room followed by ultrasound or magnetic resonance imaging will rule out hydranencephaly and hydrocephaly (see Chapter 591). An excessively large head (megalencephaly) suggests hydrocephaly, storage disease, achondroplasia, cerebral gigantism, neurocutaneous syndromes, or inborn errors of metabolism, or may be familial. The skull of a premature infant may suggest hydrocephaly because of the relatively larger brain growth in comparison with growth of other organs. Depression of the skull (indentation, fracture, ping pong ball deformity) is usually of prenatal onset and a result of prolonged focal

<table>
<thead>
<tr>
<th>Table 94-1</th>
<th>Disorders Associated with a Large Anterior Fontanel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achondroplasia</td>
<td>Apert syndrome</td>
</tr>
<tr>
<td>Athyrotic hypothyroidism</td>
<td>Cleidocranial dysostosis</td>
</tr>
<tr>
<td>Congenital rubella syndrome</td>
<td>Hallermann-Streiff syndrome</td>
</tr>
<tr>
<td>Hydrocephaly</td>
<td>Hypophosphatasia</td>
</tr>
<tr>
<td>Intrauterine growth restriction</td>
<td>Kenny syndrome</td>
</tr>
<tr>
<td>Osteogenesis imperfecta</td>
<td>Prematurity</td>
</tr>
<tr>
<td>Pyknodysostosis</td>
<td>Russell-Silver syndrome</td>
</tr>
<tr>
<td>Trisomies 13-, 18-, and 21</td>
<td>Vitamin D deficiency rickets</td>
</tr>
</tbody>
</table>

![Figure 94-1 Infant with intrauterine growth retardation as a result of placental insufficiency. Note the long, thin appearance with peeling, parchment-like dry skin, alert expression, meconium staining of the skin, and long nails. (From Clifford S: Advances in pediatrics, vol 9, Chicago, 1962, Year Book.)](Image)
pressure by the bony pelvis. Atrophic or alopecic scalp areas may represent aplasia cutis congenita, which may be sporadic, or autosomal dominant, or associated with trisomy 13, chromosome 4 deletion, or Johanson-Blizzard syndrome. Deformational plagiocephaly may be the result of in utero positioning forces on the skull and manifests as an asymmetric skull and face with ear malalignment (see Chapter 592). It is associated with torticollis and vertex positioning.

FACE

The general appearance of the face should be noted with regard to dysmorphic features, such as epicanthal folds, widely or narrowly spaced eyes, microphthalamos, asymmetry, long philtrum, and low-set ears, which are often associated with congenital syndromes. The face may be asymmetric as a result of a 7th nerve palsy, hypoplasia of the depressor muscle at the angle of the mouth, or an abnormal fetal posture (see Chapter 108); when the jaw has been held against a shoulder or an extremity during the intrauterine period, the mandible may deviate strikingly from the midline. Symmetrical facial palsy suggests absence or hypoplasia of the 7th nerve nucleus ( Möbius syndrome).

Eyes

The eyes often open spontaneously if the infant is held up and tipped gently forward and backward. This maneuver, a result of labyrinthine and neck reflexes, is more successful for inspecting the eyes than is forcing the lids apart. Conjunctival and retinal hemorrhages are usually benign. Retinal hemorrhages are more common with vacuum- or forceps-assisted deliveries, than spontaneous vaginal delivery, and least common after cesarean section. They are usually bilateral, intraretinal, and in the posterior pole. They resolve in most infants by 2 wk of age (85%) and in all infants by 4 wk. Pupillary reflexes are present after 28-30 wk of gestation. The iris should be inspected for colobomas and heterochromia. A cornea >1 cm in diameter in a term infant (with photophobia and tearing) suggests congenital glaucoma and requires prompt ophthalmologic consultation. The presence of bilateral red reflexes suggests the absence of cataracts and intraocular pathology (see Chapters 619, 627-633). Leukokoria (white pupillary reflex) suggests cataracts, tumor, chorioretinitis, retinopathy of prematurity, or a persistent hyperplastic primary vitreous and warrants an immediate ophthalmologic consultation.

Ears

Deformities of the pinnae are occasionally seen. Unilateral or bilateral preauricular skin tags occur frequently; if pedunculated, they can be tightly ligated at the base, resulting in dry gangrene and sloughing. The tympanic membrane, easily seen otoscopically through the short and straight external auditory canal, normally appears dull gray.

Nose

The nose may be slightly obstructed by mucus accumulated in the narrow nostrils. The nares should be symmetric and patent. Dislocation of the nasal cartilage from the vomerian groove results in asymmetry of the nasal passages secondary to unilateral or bilateral choanal atresia results in respiratory distress.

Mouth

A normal mouth may rarely have precocious dentition, with natal (present at birth) or neonatal (eruption after birth) teeth in the lower incisor position or aberrantly placed; these teeth are shed before the deciduous ones erupt (see Chapter 307). Alternatively, such teeth occur (present at birth) or neonatal (eruption after birth) teeth in the lower incisor position or aberrantly placed; these teeth are shed before the deciduous ones erupt (see Chapter 307). Alternatively, such teeth occur. The general appearance of the mouth may rarely have precocious dentition, with natal (present at birth) or neonatal (eruption after birth) teeth in the lower incisor position or aberrantly placed; these teeth are shed before the deciduous ones erupt (see Chapter 307). Alternatively, such teeth occur, extrac- deciduous ones erupt (see Chapter 307). Alternatively, such teeth occur, extrac deciduous ones erupt (see Chapter 307). Alternatively, such teeth occur.

NECK

The neck appears relatively short. Abnormalities are not common but include goiter, cystic hygroma, branchial cleft rests, teratoma, hemangioma, and lesions of the sternocleidomastoid muscle that are presumably traumatic or due to a fixed positioning in utero that produces either a hematoma or fibrosis, respectively. Congenital torticollis causes the head to turn toward and the face to turn away from the affected side. Plagiocephaly, facial asymmetry, and hemihypoplasia may develop if it is untreated (see Chapter 592.1). Redundant skin or webbing in a female infant suggests intrauterine lymphedema and Turner syndrome (see Chapters 81 and 586). Both clavicles should be palpated for fractures.

CHEST

Breast hypertrophy is common, and milk may be present (but should not be expressed). Asymmetry, erythema, induration, and tenderness suggest mastitis or a breast abscess. Supernumerary nipples, inverted nipples, or widely spaced nipples with a shield-shaped chest may be seen; the last finding suggests Turner syndrome.

LUNGS

Much can be learned by observing breathing. Normal variations in rate and rhythm are characteristic and fluctuate according to the infant’s physical activity, the state of wakefulness, or the presence of crying. Because fluctuations are rapid, the respiratory rate should be counted for a full minute with the infant in the resting state, preferably asleep. Under these circumstances, the usual rate for normal term infants is 30-60 breaths/min; in premature infants the rate is higher and fluctuates more widely. A rate consistently greater than 60 breaths/min during periods of regular breathing that persists for more than an hour after birth is an indication to rule out pulmonary, cardiac, or metabolic disease (acidosis) etiologies. Preterm infants may breathe with a Cheyne-Stokes rhythm, known as periodic respiration, or with complete irregularity. Irregular gasping, sometimes accompanied by spasmodic movements of the mouth and chin, strongly indicates serious impairment of the respiratory centers.

The breathing of newborn infants at rest is almost entirely diaphragmatic, so during inspiration, the soft front of the thorax is usually drawn inward while the abdomen protrudes. If the baby is quiet, relaxed, and with good color, this "paradoxic movement" does not necessarily signify insufficient ventilation. On the other hand, labored respiration with retractions is important evidence of respiratory distress syndrome, pneumonia, anomalies, or mechanical disturbance of the lungs. A weak persistent or intermittent groaning, whining cry, or grunting during expiration can signify potentially serious cardiopulmonary disease or sepsis and warrants immediate attention. When benign, the grunting resolves between 30 and 60 min after birth. Frowning of the alae nasi and retraction of the intercostal muscles and sternum are common signs of pulmonary pathology.
Normally, the breath sounds are bronchovesicular. Susception of pulmonary pathology because of diminished breath sounds, rhonchi, retractions, or cyanosis should always be verified with a chest radiograph.

**HEART**

Normal variation in the size and shape of the chest makes it difficult to estimate the size of the heart. The location of the heart should be determined to detect dextrocardia. Transitory murmurs usually represent a closing ductus arteriosus. Although congenital heart disease may not initially produce a murmur, a substantial portion of infants in whom persistent murmurs are detected during routine neonatal examination have underlying malformation. Evaluation of the heart by echocardiography is essential when the possibility of a significant lesion exists, particularly if oxygen saturations are below 95%.

The pulse is usually 110-140 beats/min at rest, but may vary normally from 90 beats/min in relaxed sleep to 180 beats/min during activity. The still higher rate of supraventricular tachycardia (＞220 beats/min) may be determined better with a cardiac monitor or electrocardiogram than by auscultation. Preterm infants usually have a higher resting heart rate, up to about 160 beats/min, but may have a sudden onset of sinus bradycardia secondary to apnea. On both admission to and discharge from the nursery, the infant's pulses should be palpated in the upper and lower extremities to detect coarctation of the aorta.

Blood pressure measurements may be a valuable diagnostic aid in ill infants (see Chapter 425). The oscillometric method is the easiest and most accurate noninvasive method available. Continuous direct measurement of blood pressure with an umbilical artery catheter may be indicated in special circumstances for critically ill infants in an intensive care unit (Fig. 94-2).

**ABDOMEN**

The liver is usually palpable, sometimes as much as 2 cm below the rib margin. Less commonly, the tip of the spleen may be felt. The approximate size and location of each kidney can usually be determined on deep palpation. At no other period of life does the amount approximate size and location of each kidney can usually be determined to and discharge from the nursery, the infant’s pulses should be palpated in the upper and lower extremities to detect coarctation of the aorta.

Blood pressure measurements may be a valuable diagnostic aid in ill infants (see Chapter 425). The oscillometric method is the easiest and most accurate noninvasive method available. Continuous direct measurement of blood pressure with an umbilical artery catheter may be indicated in special circumstances for critically ill infants in an intensive care unit (Fig. 94-2).

**GENITALS**

The genitals and mammary glands normally respond to transplacentally acquired maternal hormones to produce enlargement and secretion of the breasts in both sexes and prominence of the genitals in females, often with considerable nonpurulent discharge. These transitory manifestations require no intervention.

An imperforate hymen or other causes of vaginal obstruction may result in hydrometrocolpos and a lower abdominal mass. A normal scrotum at term is relatively large; its size may be increased by the trauma of breech delivery or by a transitory hydrocele, which is distinguished from a hernia by palpation and transillumination. The testes should be in the scrotum or should be palpable in the canals in term infants. Black male infants usually have dark pigmentation of the scrotum, because this finding may be the first evidence of adrenogenital syndrome (see Chapter 576). Erection of the penis is common and has temporary manifestations require no intervention.

The prepuc of a newborn infant is normally tight and adherent. Severe hypospadias or epispadias should always lead one to suspect either that abnormal sex chromosomes are present (see Chapter 81) or that the infant is actually a masculinized female with an enlarged clitoris, because this finding may be the first evidence of adrenogenital syndrome (see Chapter 576). Erection of the penis is common and has no significance. Urine is usually passed during or immediately after birth; a period without voiding may normally follow. Most neonates void by 12 hr, and approximately 95% of preterm and term infants void within 24 hr.

**ANUS**

Some passage of meconium usually occurs within the 1st 12 hr after birth; 99% of term infants and 95% of premature infants pass meconium within 48 hr of birth. Imperforate anus is not always visible and may require evidence obtained by gentle insertion of the examiner’s little finger or a rectal tube. Radiographic study is required. Passage of meconium does not rule out an imperforate anus if a rectal–vaginal fistula is present. The dimple or irregularity in skinfold often normally
present in the sacrococcygeal midline may be mistaken for an actual or potential neurocutaneous sinus.

**EXTREMITIES**

During examination of the extremities, the effects of fetal posture (see Chapter 672) should be noted so that their cause and usual transitory nature can be explained to the mother. Such explanations are particularly important after breech presentations. A fracture or nerve injury associated with delivery can be detected more commonly by observation of the extremities in spontaneous or stimulated activity than by any other means. The hands and feet should be examined for polydactyly, syndactyly, and abnormal dermatoglyphic patterns such as a simian crease.

The hips of all infants should be examined with specific maneuvers to rule out congenital dislocation (see Chapter 678.1).

**NEUROLOGIC EXAMINATION**

See Chapters 9 and 590.

In utero neuromuscular diseases associated with limited fetal motion produce a constellation of signs and symptoms that are independent of the specific disease. Severe positional deformations and contractures produce arthrogryposis. Other manifestations of fetal neuromuscular disease include breech presentation, polyhydramnios, failure to breathe at birth, pulmonary hypoplasia, dislocated hips, undescended testes, thin ribs, and clubfoot. Many congenital disorders manifest as hypotonia, hypertonia, or seizures.

Bibliography is available at Expert Consult.

### 94.3 Routine Delivery Room and Initial Care

**Waldemar A. Carlo**

Low-risk infants may initially be placed on the mother’s abdomen after delivery; clearing the mouth of secretions with gentle suction with a bulb syringe or soft catheter is indicated if there is an excessive (copious) amount of fluid in the mouth or nares. In resource-poor countries, gentle wiping of the face, nose, and mouth with a soft cloth may be equally effective as a bulb syringe. Nonetheless, spontaneously breathing neonates with no distress do not need any assisted method to clear their airway. Most healthy infants who appear to be in satisfactory condition should be given direct to their mothers for immediate bonding and nursing. Delayed clamping of the umbilical cord (~30 sec) has value in reducing the incidence of anemia in infancy. If respiratory distress is a concern, infants should be placed under warmers for observation.

The **Apgar score** is a practical method of systematically assessing newborn infants immediately after birth (Table 94-2). A low score may be the result of fetal distress but may also be caused by a number of factors, including prematurity and drugs given to the mother during labor (Table 94-3). The Apgar score was not designed to predict neurologic outcome. Indeed, the score is normal in most patients in whom cerebral palsy subsequently develops, and the incidence of cerebral palsy is low in infants with Apgar scores of 0-3 at 5 min (but higher than in infants with Apgar scores of 7-10). Low Apgar scores and umbilical artery blood pH predict neonatal death. An Apgar score of 0-3 at 5 min is uncommon but is a better predictor of neonatal death (in both term and preterm infants) than an umbilical artery pH ≤7.0; the presence of both variables increases the relative risk of neonatal mortality in term and preterm infants (Table 94-4). Infants who fail to initiate respiration should receive prompt resuscitation and close observation (see Chapter 100).

### MAINTENANCE OF BODY HEAT

Newborn infants are at risk for heat loss and hypothermia for several reasons. Relative to body weight, the body surface area of a newborn infant is approximately 3 times that of an adult. Generation of body heat depends in large part on body weight, but heat loss depends on surface area. In low birthweight and preterm infants, the insulating layer of subcutaneous fat is thin. The estimated rate of heat loss in a newborn is approximately 4 times that of an adult. Under the usual delivery room conditions (20-25°C [68-77°F]), an infant’s skin temperature falls approximately 0.3°C (0.5°F)/min and deep body temperature decreases approximately 0.1°C (0.18°F)/min during the period immediately after delivery; these rates generally result in a

<table>
<thead>
<tr>
<th>Fahrenheit</th>
<th>Celsius</th>
</tr>
</thead>
<tbody>
<tr>
<td>72°F</td>
<td>22°C</td>
</tr>
<tr>
<td>77°F</td>
<td>25°C</td>
</tr>
</tbody>
</table>

**Table 94-2** Apgar Evaluation of Newborn Infants

<table>
<thead>
<tr>
<th>SIGN</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>Absent</td>
<td>Below 100</td>
<td>Over 100</td>
</tr>
<tr>
<td>Respiratory effort</td>
<td>Absent</td>
<td>Slow, irregular</td>
<td>Good, crying</td>
</tr>
<tr>
<td>Muscle tone</td>
<td>Limp</td>
<td>Some flexion of extremities</td>
<td>Active motion</td>
</tr>
<tr>
<td>Response to catheter in nostril (tested after oropharynx is clear)</td>
<td>No response</td>
<td>Grimace</td>
<td>Cough or sneeze</td>
</tr>
<tr>
<td>Color</td>
<td>Blue, pale</td>
<td>Body pink, extremities blue</td>
<td>Completely pink</td>
</tr>
</tbody>
</table>

*Sixty sec after complete birth of the infant (disregarding the cord and placenta), the 5 objective signs listed here are evaluated, and each is given a score of 0, 1, or 2. A total score of 10 indicates an infant in the best possible condition. An infant with a score of 0-3 requires immediate resuscitation.


### Table 94-3 Factors Affecting the Apgar Score

<table>
<thead>
<tr>
<th>FALSE-POSITIVE (NO FETAL ACIDOSIS OR HYPOXIA; LOW APGAR SCORE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurity</td>
</tr>
<tr>
<td>Magnesium sulfate</td>
</tr>
<tr>
<td>Precipitous delivery</td>
</tr>
<tr>
<td>Congenital neuropathy</td>
</tr>
<tr>
<td>Central nervous system anomaly</td>
</tr>
<tr>
<td>Airway obstruction (choanal atresia)</td>
</tr>
<tr>
<td>Previous episodes of fetal asphyxia (recovered)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FALSE-NEGATIVE (ACIDOSIS; NORMAL APGAR SCORE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal acidosis</td>
</tr>
<tr>
<td>Some full-term infants</td>
</tr>
</tbody>
</table>

*Regardless of the etiology, a low Apgar score because of fetal asphyxia, immaturity, central nervous system depression, or airway obstruction identifies an infant needing immediate resuscitation.
Bibliography
cumulative loss of 2-3°C (3.6-5.4°F) in deep body temperature (corresponding to a heat loss of approximately 200 kcal/kg). The heat loss occurs by 4 mechanisms: (1) convection of heat energy to the cooler surrounding air, (2) conduction of heat to the colder materials touching the infant, (3) heat radiation from the infant to other nearby cooler objects, and (4) evaporation from skin and lungs.

Metabolic acidosis, hypoxemia, hypoglycemia, and increased renal excretion of water and solutes may develop in term infants exposed to cold after birth because of their effort to compensate for heat loss. Heat production is augmented by increasing the metabolic rate and oxygen consumption in part by releasing norepinephrine, which results in nonshivering thermo-generation through oxidation of fat, particularly brown fat. In addition, muscular activity may increase. Hypoglycemic or hypoxic infants cannot increase their oxygen consumption when exposed to a cold environment, and their central temperature decreases. After labor and vaginal delivery, many newborn infants have mild to moderate metabolic acidosis, for which they may compensate by hyperventilating, a response that is more difficult for infants with central nervous system depression (asphyxia, drugs) and infants exposed to cold stress in the delivery room. Therefore, to reduce heat loss, it is desirable to ensure that infants are dried and either wrapped in blankets or placed with the mother or under radiant warmers. Skin-to-skin contact with the mother is the optimal method of maintaining temperature in the stable newborn. Because carrying out resuscitative measures on a covered infant or one enclosed in an incubator is difficult, a radiant heat source should be used to warm the baby during resuscitation.

**ANTISEPTIC SKIN AND CORD CARE**

Careful removal of the amniotic fluid and blood from the skin shortly after birth may reduce the risk of infection with bloodborne agents. Once a healthy infant’s temperature has stabilized, the entire skin and cord should be cleansed with warm water or a mild nonmedicated soap solution and rinsed with water to reduce the incidence of skin and periumbilical colonization with pathogenic bacteria and subsequent infectious complications. To avoid heat loss, the infant is then dried and wrapped in clean blankets. To reduce colonization with *Staphylococcus aureus* and other pathogenic bacteria, the umbilical cord may be treated daily with a bactericidal or antimicrobial agents such as chlorhexidine, triple dye, or bacitracin. One application of triple dye followed by twice-daily alcohol swabbing (until the cord falls off) reduces colonization, exudates, and foul odor of the umbilicus in comparison with dry care (soap and water when soiled). On the rare occasion of *S. aureus* nursery epidemics, a single hexachlorophene bath may be used. Topical ointments should not be applied to preterm infants in neonatal intensive care units because this treatment increases the risk of bacterial sepsis. Routine or repeated total-body exposure to hexachlorophene may be neurotoxic, particularly in low-birthweight infants, and is thus contraindicated. Nursery personnel should use alcohol-based solutions or chlorhexidine or iodophor-containing antiseptic soaps for routine handwashing before caring for each infant. Rigid enforcement of hand-to-elbow washing for 2 min in the initial wash and 15-30 sec in subsequent washes is essential for staff and visitors entering the nursery.

**OTHER MEASURES**

The eyes of all infants, including those born by cesarean section, must be protected against gonococcal ophthalmia neonatorum by application of a 1-cm ribbon of erythromycin (0.5%) or tetracycline (1.0%) sterile ophthalmic ointments in each lower conjunctival sac. This procedure may be delayed during the initial short-alert period after birth to promote bonding, but once applied, drops should not be rinsed out (see Chapters 192 and 226.3). A 1% silver nitrate solution is an acceptable alternative, but leads to a transient chemical conjunctivitis in 10-20% of cases.

Although hemorrhage in newborn infants can be a result of factors other than vitamin K deficiency, an intramuscular injection of 0.5-1 mg of water-soluble vitamin K₁ (phytonadione) should be given to all infants shortly after birth to prevent hemorrhagic disease of the newborn (see Chapter 103.4). Oral vitamin K is not as effective as the parenteral dosage.

Hepatitis B immunization before discharge from the nursery is recommended for newborns with weight >2 kg irrespective of maternal hepatitis status.

Neonatal screening is available for various genetic, metabolic, hemato logic, and endocrine disorders. All states in the United States have adopted the Advisory Committee on Heritable Disorders in Newborns and Children, although the specific tests performed vary by state based in part to disease prevalence, detection rates, and costs (see Chapter 84). The most commonly identified disorders (and their rates) include hypothyroidism (52/100,000 births), cystic fibrosis (30/100,000), hemoglobinopathies (26/100,000), medium-chain acyl–coenzyme A dehydrogenase deficiency (6/100,000), galactosemia (5/100,000), phenylketonuria (5/100,000), and adrenal hyperplasia (5/100,000). To be effective in the timely identification and prompt management of treatable diseases, screening programs must include not only high-quality laboratory tests but also follow-up of infants with abnormal test results; education, counseling, and psychologic support for families; and prompt referral of the identified neonate for accurate diagnosis and appropriate treatment.

Hearing impairment, a serious morbidity that affects speech and language development, may be severe in 2/1,000 births and overall affects 5/1,000 births. Universal screening of infants is recommended to ensure early detection of hearing loss and appropriate, timely intervention.

Universal screening with pulse oximetry provides early detection of ductal dependent cyanotic congenital heart disease (see Chapter 425). Universal screening for hyperbilirubinemia should include risk assessment in all infants with measurement of serum or transcutaneous bilirubin levels before hospital discharge.

Universal screening for congenital hip dysplasia with physical examination with the Ortolani (sensation of the dislocated hip reducing) and Barlow (unstable hip dislocating from the acetabulum) tests is recommended but routine hip ultrasound is not indicated.

Routine measurement of the hematocrit or blood glucose value is not necessary in the absence of risk factors.

**Bibliography is available at Expert Consult.**

94.4 Nursery Care

**Waldemar A. Carlo**

Non–high-risk, healthy infants may be taken to the “regular” (normal) newborn nursery or may be placed in the mother’s room if the hospital has rooming-in facilities.
Bibliography
The bassinet, preferably of clear plastic to allow for easy visibility and care, should be cleaned frequently. All professional care should be given to the infant in the bassinet, including the physical examination, clothing changes, temperature taking, skin cleansing, and other procedures that, if performed elsewhere, would establish a common contact point and possibly provide a channel for cross infection. The clothing and bedding should be minimal, only enough needed for an infant's comfort; the nursery temperature should be kept at approximately 22-26°C (72-78°F). The infant's temperature should be taken at least every 2 hours and axillary temperature 36.1-37°C (97.0-98.6°F) in open crib. The perineal area can be cleaned with baby wipes or with mild soap and warm water. Meconium or feces should be cleansed from the buttocks with sterile cotton moistened with sterile water. The foreskin of a male infant should not be retracted.

Infants should meet minimum criteria before hospital discharge (Table 94-5). Late preterm infants (34-36 wk) and infants with early discharge (<48 hr) or very early discharge (<24 hr) are at increased risk of rehospitalization. Early discharge requires careful ambulatory follow-up at home (by a visiting nurse) or in the office within 48 hr of discharge.

**Table 94-5** Criteria for Discharge from the Normal Newborn Nursery

<table>
<thead>
<tr>
<th>Uncomplicated antepartum, intrapartum, postpartum courses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal delivery</td>
</tr>
<tr>
<td>Singleton at 38-42 wk: appropriate for gestational age</td>
</tr>
<tr>
<td>Normal vital signs including respiratory rate &lt;60 breaths/min; axillary temperature 36.1-37°C (97.0-98.6°F) in open crib</td>
</tr>
<tr>
<td>Normal physical examination reveals no abnormalities requiring continued hospitalization</td>
</tr>
<tr>
<td>Urination; stool = 1</td>
</tr>
<tr>
<td>At least 2 uneventful, successful feedings</td>
</tr>
<tr>
<td>No excessive bleeding 2 hr after circumcision</td>
</tr>
<tr>
<td>No jaundice within 24 hr of birth; if jaundice, appropriate management and follow-up are in place</td>
</tr>
<tr>
<td>Evidence of parental knowledge, ability, and confidence to care for the baby at home:</td>
</tr>
<tr>
<td>Feeding</td>
</tr>
<tr>
<td>Cord, skin, genital care</td>
</tr>
<tr>
<td>Recognition of illness (jaundice, poor feeding, lethargy, fever, etc.)</td>
</tr>
<tr>
<td>Infant safety (car seat, supine sleep position, etc.)</td>
</tr>
<tr>
<td>Availability of family and physician support (physician follow-up)</td>
</tr>
<tr>
<td>Laboratory evaluation:</td>
</tr>
<tr>
<td>Syphilis</td>
</tr>
<tr>
<td>Hepatitis B surface antigen and vaccination or appointment for vaccination</td>
</tr>
<tr>
<td>Coombs test and blood type if clinically indicated</td>
</tr>
<tr>
<td>Expanded metabolic screening: phenylketonuria, thyroid, galactosemia, sickle cell</td>
</tr>
<tr>
<td>Hearing screening</td>
</tr>
<tr>
<td>No social risks:</td>
</tr>
<tr>
<td>Substance abuse</td>
</tr>
<tr>
<td>History of child abuse</td>
</tr>
<tr>
<td>Domestic violence</td>
</tr>
<tr>
<td>Mental illness</td>
</tr>
<tr>
<td>Teen mother</td>
</tr>
<tr>
<td>Homelessness</td>
</tr>
<tr>
<td>Barriers to follow-up</td>
</tr>
</tbody>
</table>

*It is not likely that all these criteria will be met before 48 hr of age.


**Bibliography is available at Expert Consult.**

### 94.5 Parent–Infant Bonding

*Waldemar A. Carlo*

See also Chapter 9.

Normal infant development depends partly on a series of affectionate responses exchanged between a mother and her newborn infant that binds them psychologically and physiologically. This bonding is facilitated and reinforced by the emotional support of a loving family. The attachment process may be important in enabling some mothers to provide loving care during the neonatal period and subsequently during childhood. The power of this attachment is so great that it enables the mother and the father to make unusual sacrifices necessary for the day-to-day care of the infant, care night after night, giving feedings 24 hr a day, attending to crying, and so on. The sacrifices continue for many years as parents dedicate much of their lives to their children.

Parent–infant bonding is initiated before birth with the planning and confirmation of the pregnancy. Subsequently, there is a growing awareness of the baby as an individual, starting usually with the remarkably powerful event of "quickening" or sensation of fetal movements. After delivery and during the ensuing weeks, sensory (visual, auditory, olfactory) and physical contact between the mother and baby triggers various mutually rewarding and pleasurable interactions, such as the mother touching the infant's extremities and face with her fingertips and encompassing and gently massaging the infant's trunk with her hands. Touching an infant's cheek elicits responsive turning toward the mother's face or toward the breast with nuzzling and licking of the nipple, a powerful stimulus for prolactin secretion. An infant's initial quiet alert state provides the opportunity for eye-to-eye contact, which is particularly important in stimulating the loving and possessive feelings of many parents for their babies. An infant's crying elicits the maternal response of touching the infant and speaking in a soft, soothing, higher-toned voice. Initial contact between the mother and infant should take place in the delivery room, and opportunities for extended intimate contact and breastfeeding should be provided within the 1st hours after birth. Delayed or abnormal maternal–infant bonding, as occurs because of prematurity, infant or maternal illness, birth defects, or family stress, may harm infant development and maternal caretaking ability. Hospital routines should be designed to encourage parent–infant contact. Open nurseries, rooming-in arrangements, care by parents, and family-centered care increase the opportunities for better parent–infant interaction.

### Nurseries and Breastfeeding

See Chapter 45 for full discussions of breastfeeding and formula feeding.

Ample evidence indicates that there are infant and maternal benefits to breastfeeding. Practices that encourage successful breastfeeding include antepartum education and encouragement, immediate postpartum mother–infant contact with suckling, rooming-in arrangements, demand feeding, inclusion of fathers in breastfeeding education, and support from experienced women. Nursing at first for at least 5 min at each breast is reasonable, allows a baby to obtain most of the available breast contents, and provides effective stimulation for increasing the milk supply. Nursing episodes should then be extended according to the comfort and desire of the mother and infant. A confident and relaxed mother, supported by an encouraging home and hospital environment, is likely to nurse well. The Baby-Friendly Hospital Initiative, a global effort (sponsored by the World Health Organization and the United Nations Children's Fund) to promote breastfeeding, recommends 10 steps to successful breastfeeding (Table 94-6). Some hospital practices contribute to difficulties in breastfeeding by enforcing 4-hr feeding schedules, limiting nursing time, using only 1 breast at a
Bibliography
feeding, washing nipples with substances other than water, delaying the first feeding, providing formula supplements, and using heavy intrapartum sedation.

**DRUGS AND BREASTFEEDING**

Maternal medications may affect the production and safety of breast milk (Table 94-7). Although most commonly used medications are safe, the safety of any new drug to be used while a woman is breastfeeding must be confirmed before the drug is initiated and/or breastfeeding is continued. Maternal sedatives may result in sedation of the infant. Maternal drugs that are weak acids, composed of large molecules, plasma bound, or poorly absorbed from the maternal or neonatal intestine are less likely to affect a neonate.

**CONTRAINDICATIONS TO BREASTFEEDING**

Medical contraindications to breastfeeding in the United States include infants with galactosemia, maple syrup urine disease, and phenylketonuria. Maternal conditions that contraindicate breastfeeding include infection with HIV, human T-cell lymphotropic virus types 1 and 2, active tuberculosis (until appropriately treated and not considered contagious), herpes virus infection on breast, and maternal treatment with some radioactive compounds (Table 94-8).

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### Table 94-6  
**Ten Steps to Successful Breastfeeding**

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Have a written breastfeeding policy that is routinely communicated to all healthcare staff.</td>
</tr>
<tr>
<td>2.</td>
<td>Train all healthcare staff in the skills necessary to implement this policy.</td>
</tr>
<tr>
<td>3.</td>
<td>Inform all pregnant women about the benefits and management of breastfeeding.</td>
</tr>
<tr>
<td>4.</td>
<td>Help mothers initiate breastfeeding within a half hour of birth.</td>
</tr>
<tr>
<td>5.</td>
<td>Show mothers how to breastfeed and how to maintain lactation even if they should be separated from their infants.</td>
</tr>
<tr>
<td>6.</td>
<td>Give newborn infants no food or drink other than breast milk unless medically indicated.</td>
</tr>
<tr>
<td>7.</td>
<td>Practice rooming-in (allow mothers and infants to remain together) 24 hr a day.</td>
</tr>
<tr>
<td>8.</td>
<td>Encourage breastfeeding on demand.</td>
</tr>
<tr>
<td>9.</td>
<td>Give no artificial teats or pacifiers (also called dummies or soothers) to breastfeeding infants.</td>
</tr>
<tr>
<td>10.</td>
<td>Foster the establishment of breastfeeding support groups and refer mothers to them on discharge from the hospital or clinic.</td>
</tr>
</tbody>
</table>


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### Table 94-7  
**Drugs and Breastfeeding**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Contraindicated Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drugsmetabolites</td>
</tr>
<tr>
<td>Maternal medications</td>
<td></td>
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<tr>
<td></td>
<td>Amphetamines</td>
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<tr>
<td></td>
<td>Antineoplastic agents</td>
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<tr>
<td></td>
<td>Bromocriptine</td>
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<tr>
<td></td>
<td>Chloramphenicol</td>
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<tr>
<td></td>
<td>Clozapine</td>
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<tr>
<td></td>
<td>Cocaine</td>
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<tr>
<td></td>
<td>Cyclophosphamide</td>
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<tr>
<td></td>
<td>Diethylstilbestrol</td>
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<tr>
<td></td>
<td>Doxorubicin</td>
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<td>Ecstasy</td>
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<td></td>
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<td>Gold salts</td>
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<tr>
<td></td>
<td>Heroin</td>
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<td></td>
<td>Immunosuppressants</td>
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<td></td>
<td>Lactase</td>
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<tr>
<td></td>
<td>Methimazole</td>
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<tr>
<td></td>
<td>Methamphetamine</td>
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<tr>
<td></td>
<td>Phencyclidine (PCP)</td>
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<tr>
<td></td>
<td>Radiopharmaceuticals</td>
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<tr>
<td></td>
<td>Thioracil</td>
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<td></td>
<td>Yohimbe</td>
</tr>
<tr>
<td></td>
<td>AVOID OR GIVE WITH CAUTION</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td></td>
</tr>
<tr>
<td>Anthraquinones ( laxatives)</td>
<td></td>
</tr>
<tr>
<td>Apyni (salicylates)</td>
<td></td>
</tr>
<tr>
<td>Atropine</td>
<td></td>
</tr>
<tr>
<td>B-Adrenergic blocking agents</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td></td>
</tr>
<tr>
<td>Birth control pills</td>
<td></td>
</tr>
<tr>
<td>Bromides</td>
<td></td>
</tr>
<tr>
<td>Buprenorphine/naltrexone</td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td></td>
</tr>
<tr>
<td>Calciferol</td>
<td></td>
</tr>
<tr>
<td>Cascara</td>
<td></td>
</tr>
<tr>
<td>Cephalosporin</td>
<td></td>
</tr>
<tr>
<td>Codine</td>
<td></td>
</tr>
<tr>
<td>Dicumarol</td>
<td></td>
</tr>
<tr>
<td>Dihydropyridine</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td></td>
</tr>
<tr>
<td>Estrogens</td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td></td>
</tr>
<tr>
<td>Low-molecular-weight heparins</td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td></td>
</tr>
<tr>
<td>Methadone*</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
</tr>
<tr>
<td>Muscle relaxants</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td></td>
</tr>
<tr>
<td>Propylthiouracil</td>
<td></td>
</tr>
<tr>
<td>Sedatives*</td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td></td>
</tr>
<tr>
<td>Vitamins</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
</tr>
<tr>
<td>PROBABLY SAFE</td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td></td>
</tr>
<tr>
<td>Acyclovir</td>
<td></td>
</tr>
<tr>
<td>Aldomet</td>
<td></td>
</tr>
<tr>
<td>Anesthetics</td>
<td></td>
</tr>
<tr>
<td>Antibiotics (not chloramphenicol)</td>
<td></td>
</tr>
<tr>
<td>Antiepileptics</td>
<td></td>
</tr>
<tr>
<td>Antihistamines</td>
<td></td>
</tr>
<tr>
<td>Antithyroid (not methimazole)</td>
<td></td>
</tr>
<tr>
<td>Bishydroxycoumarin (dicumarol)</td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine*</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td></td>
</tr>
<tr>
<td>Depo-Provera</td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
</tr>
<tr>
<td>Dilantin (phenytoin)</td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td></td>
</tr>
<tr>
<td>Hydralazine</td>
<td></td>
</tr>
<tr>
<td>Indomethacin, other nonsteroidal antiinflammatory drugs</td>
<td></td>
</tr>
</tbody>
</table>

*Watch for sedation.

---

### Table 94-8  
**Summary of Infectious Agents Detected in Milk and Newborn Disease**

<table>
<thead>
<tr>
<th>Infectious Agent</th>
<th>Detected in Breast Milk?</th>
<th>Breast Milk Reported as Cause of Newborn Disease?</th>
<th>Maternal Infection Contraindication to Breastfeeding?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastitis/Staphylococcus aureus</td>
<td>Yes</td>
<td>No</td>
<td>No, unless breast abscess present</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active disease</td>
<td>Yes</td>
<td>No</td>
<td>Yes, because of aerosol spread, or tuberculosis mastitis</td>
</tr>
<tr>
<td>Purified protein derivative skin test</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>chest radiograph findings negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escherichia coli, other Gram-negative</td>
<td>Yes, stored</td>
<td>Yes</td>
<td>No*</td>
</tr>
<tr>
<td>rods</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group B streptococci</td>
<td>Yes</td>
<td>Yes</td>
<td>No*</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>Yes</td>
<td>Yes</td>
<td>No*</td>
</tr>
<tr>
<td>Campylobacter jejuni</td>
<td>Yes</td>
<td>Yes</td>
<td>No*</td>
</tr>
<tr>
<td>Cronobacter sakazakii</td>
<td>Yes</td>
<td>Yes</td>
<td>No*</td>
</tr>
<tr>
<td>Syphilis</td>
<td>No</td>
<td>No</td>
<td>No*</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>No</td>
<td>No</td>
<td>No*</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>No</td>
<td>No</td>
<td>No*</td>
</tr>
<tr>
<td>Parvovirus</td>
<td>No</td>
<td>No</td>
<td>No*</td>
</tr>
<tr>
<td>Varicella</td>
<td>No</td>
<td>No</td>
<td>No*</td>
</tr>
</tbody>
</table>

*Continued
### Summary of Infectious Agents Detected in Milk and Newborn Disease—cont’d

<table>
<thead>
<tr>
<th>INFECTIOUS AGENT</th>
<th>DETECTED IN BREAST MILK?</th>
<th>BREAST MILK REPORTED AS CAUSE OF NEWBORN DISEASE?</th>
<th>MATERNAL INFECTION CONTRAINDICATION TO BREASTFEEDING?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VIRUSES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, developed countries</td>
</tr>
<tr>
<td>Cytomegalovirus:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Term infant</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Preterm infant</td>
<td>Yes</td>
<td>Yes</td>
<td>Evaluate on an individual basis</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>Yes, surface antigen</td>
<td>No</td>
<td>No, developed countries†</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>Yes</td>
<td>No</td>
<td>No§</td>
</tr>
<tr>
<td>Hepatitis E virus</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, developed countries</td>
</tr>
<tr>
<td>Human T-cell leukemia virus (HTLV)-1</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, developed countries</td>
</tr>
<tr>
<td>HTLV-2</td>
<td>Yes</td>
<td>?</td>
<td>Yes, developed countries</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>Yes</td>
<td>No/?yes</td>
<td>No, unless breast vesicles present</td>
</tr>
<tr>
<td>Rubella</td>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Wild type</td>
<td>Yes</td>
<td>Yes, rare</td>
<td>No</td>
</tr>
<tr>
<td>Vaccine</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Varicella-zoster virus</td>
<td>Yes</td>
<td>No</td>
<td>No, cover active lesions¶</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Human herpesvirus (HHV)-6</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>HHV-7</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>West Nile virus</td>
<td>Possible</td>
<td>Possible</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>PARASITES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxoplasma gondii</td>
<td>Yes</td>
<td>Yes, 1 case</td>
<td>No</td>
</tr>
</tbody>
</table>

*Provided that the mother and child are taking appropriate antibiotics.
†Treat mother and child if active disease.
‡Immunize and immune globulin at birth.
§Provided that the mother is HIV-seronegative. Mothers should be counseled that breast milk transmission of hepatitis C virus has not been documented, but is theoretically possible.
¶Provide appropriate antivaricella therapy or prophylaxis to newborn.


Donor human milk, particularly purchased through the Internet, may be contaminated with potential pathogens. Contamination is much less of a concern with unpasteurized human milk obtained from a milk bank.

Bibliography is available at Expert Consult.
Bibliography

Sachs HC, AAP Committee on Drugs: The transfer of drugs and therapeutics into human breast milk: an update on selected topics, Pediatrics 132:e796–e809, 2013.
High-risk pregnancies are those that increase the likelihood of abortion, fetal death, preterm delivery, intrauterine growth restriction, poor cardiopulmonary or metabolic transitioning at birth, fetal or neonatal disease, congenital malformations, or mental retardation and other handicaps (Table 95-1; see Chapter 96). Some factors, such as ingestion of a teratogenic drug in the 1st trimester, are causally related to the risk; others, such as hydramnios, are associations that alert a physician to determine the etiology and avoid the inherent risks associated with excessive amniotic fluid. On the basis of their history, 10-20% of pregnant women can be identified as being at high risk; nearly half of all perinatal mortality and morbidity is associated with these high-risk pregnancies. Although assessing antepartum risk is important in reducing perinatal mortality and morbidity, some pregnancies become high risk only during labor and delivery; therefore, careful monitoring is critical throughout the intrapartum course.

Identifying high-risk pregnancies is important not only because it is the first step toward prevention but also because therapeutic steps may often be taken to reduce the risks to the fetus or neonate if the physician knows of the potential for difficulty.

GENETIC FACTORS

The occurrence of chromosomal abnormalities, congenital anomalies, inborn errors of metabolism, mental retardation, or any familial disease in blood relatives increases the risk of the same condition in the infant. Because many parents recognize only obvious clinical manifestations of genetically determined diseases, specific inquiry should be made about any disease affecting 1 or more blood relatives.

MATERNAL FACTORS

The lowest neonatal mortality rate occurs in infants of mothers who receive adequate prenatal care and who are 20-30 yr of age. Pregnancies in both teenagers and women older than 40 yr, particularly primiparous women, are at increased risk for intrauterine growth restriction, fetal distress, and intrauterine death. Advanced maternal age increases the risk of both chromosomal and nonchromosomal fetal malformations (Fig. 95-1).

Maternal illness (Table 95-2), multiple pregnancies (particularly those involving monochorionic twinning), infections (Table 95-3), and certain drugs (see Chapter 96) increase the risk for the fetus. The use of assisted reproductive technology (in vitro fertilization, intracytoplasmic sperm injection) increases the risk of perinatal mortality, infant morbidity, prematurity, low and very-low birthweight, and cerebral palsy, largely because of the increase in multiple-fetus pregnancies with such technology; the risks for birth defects are also increased, in part, because of epigenetic effects on gene expression.
Preterm birth is common in high-risk pregnancies (see Chapter 97). Factors associated with prematurity, noted in Table 95-1, include biologic markers such as cervical shortening, genital infection, fetal fibronectin in cervicovaginal secretions, serum \( \alpha \)-fetoprotein, and preterm premature rupture of membranes (PROM). PROM occurs in 30-40% of preterm deliveries, and it is a leading identifiable cause of prematurity. Preterm delivery is often difficult to predict.

### Table 95-1: Factors Associated with High-Risk Pregnancy

<table>
<thead>
<tr>
<th>ECONOMIC</th>
<th>Cultural-Behavioral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poverty</td>
<td>Low educational status</td>
</tr>
<tr>
<td>Unemployment</td>
<td>Poor healthcare attitudes</td>
</tr>
<tr>
<td>Uninsured, underinsured health insurance</td>
<td>No care or inadequate prenatal care</td>
</tr>
<tr>
<td>Poor access to prenatal care</td>
<td>Cigarette, alcohol, illicit drug use</td>
</tr>
<tr>
<td></td>
<td>Age &lt;20 or &gt;40 yr</td>
</tr>
<tr>
<td></td>
<td>Unmarried</td>
</tr>
<tr>
<td></td>
<td>Short interpregnancy interval</td>
</tr>
<tr>
<td></td>
<td>Lack of support group (husband, family, religion)</td>
</tr>
<tr>
<td></td>
<td>Stress (physical, psychologic)</td>
</tr>
<tr>
<td></td>
<td>Black race</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>BIOLOGIC-GENETIC</td>
</tr>
<tr>
<td></td>
<td>Previous low birthweight or preterm infant</td>
</tr>
<tr>
<td></td>
<td>Low weight for height</td>
</tr>
<tr>
<td></td>
<td>Poor weight gain during pregnancy</td>
</tr>
<tr>
<td></td>
<td>Short stature</td>
</tr>
<tr>
<td></td>
<td>Poor nutrition</td>
</tr>
<tr>
<td></td>
<td>Consanguinity</td>
</tr>
<tr>
<td></td>
<td>Intergenerational effects</td>
</tr>
<tr>
<td></td>
<td>Low maternal birthweight</td>
</tr>
<tr>
<td></td>
<td>Hereditary diseases (inborn error of metabolism)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>REPRODUCTIVE</td>
</tr>
<tr>
<td></td>
<td>Previous cesarean section</td>
</tr>
<tr>
<td></td>
<td>Previous infertility</td>
</tr>
<tr>
<td></td>
<td>Conception by reproductive technology</td>
</tr>
<tr>
<td></td>
<td>Prolonged gestation</td>
</tr>
<tr>
<td></td>
<td>Prolonged labor</td>
</tr>
<tr>
<td></td>
<td>Previous infant with cerebral palsy, mental retardation, birth trauma, congenital anomalies</td>
</tr>
<tr>
<td></td>
<td>Abnormal lie (breach)</td>
</tr>
<tr>
<td></td>
<td>Multiple gestations</td>
</tr>
<tr>
<td></td>
<td>Premature rupture of membranes</td>
</tr>
<tr>
<td></td>
<td>Infection (systemic, amniotic, extra-amniotic, cervical)</td>
</tr>
<tr>
<td></td>
<td>Preeclampsia or eclampsia</td>
</tr>
<tr>
<td></td>
<td>Uterine bleeding (abruptio placentae, placenta previa)</td>
</tr>
<tr>
<td></td>
<td>Parity (0 or &gt;5 previous deliveries)</td>
</tr>
<tr>
<td></td>
<td>Uterine or cervical anomalies</td>
</tr>
<tr>
<td></td>
<td>Fetal disease</td>
</tr>
<tr>
<td></td>
<td>Abnormal fetal growth</td>
</tr>
<tr>
<td></td>
<td>Idiopathic premature labor</td>
</tr>
<tr>
<td></td>
<td>Iatrogenic prematurity</td>
</tr>
<tr>
<td></td>
<td>High or low levels of maternal serum ( \alpha )-fetoprotein</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MEDICAL</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>Congenital heart disease</td>
</tr>
<tr>
<td></td>
<td>Autoimmune disease</td>
</tr>
<tr>
<td></td>
<td>Sickle cell anemia</td>
</tr>
<tr>
<td></td>
<td>Intercurrent surgery or trauma</td>
</tr>
<tr>
<td></td>
<td>Sexually transmitted infection</td>
</tr>
<tr>
<td></td>
<td>Maternal hypercoagulable states</td>
</tr>
<tr>
<td></td>
<td>Exposure to prescription medications</td>
</tr>
<tr>
<td></td>
<td>TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex) infection</td>
</tr>
</tbody>
</table>

Polyhydramnios and oligohydramnios indicate high-risk pregnancies. Although the turnover rate of amniotic fluid is rapid, during normal pregnancy the amniotic fluid volume gradually increases at a rate of <10 mL/day until about the 34th wk of pregnancy, after which it slowly diminishes. Volumes vary widely in normal pregnancy; term volume may be 500-2000 mL. A volume estimated at greater than 2000 mL in the 3rd trimester constitutes polyhydramnios, and a volume estimated at <500 mL indicates oligohydramnios. Polyhydramnios complicates 1-3%, and oligohydramnios 1-5%, of pregnancies. The ultrasonographic criteria for these diagnoses are based on the amniotic fluid index, which is determined by measuring the vertical diameter of amniotic fluid pockets in four quadrants; an index >24 cm suggests polyhydramnios, whereas an index <5 cm suggests oligohydramnios.

Acute polyhydramnios is rare and is usually associated with preterm labor and delivery. Chronic polyhydramnios is diagnosed in the 3rd trimester from the discrepancy between uterine size and gestational age; it is occasionally not diagnosed until the patient has dysfunctional labor or an abnormally large amount of amniotic fluid is noted during delivery. Polyhydramnios is associated with preterm labor, abruptio placentae, multiple congenital anomalies, and fetal neuromuscular dysfunction or obstruction of the gastrointestinal tract that interferes with reabsorption of the amniotic fluid that is normally swallowed by the fetus (Table 95-1). Increased fetal urination or edema formation is also associated with excessive amniotic fluid volume. Ultrasound demonstrates the increased amniotic fluid surrounding the fetus and detects associated fetal anomalies, hydrops, pleural effusions, and ascites. In 60% of patients, no cause is identified. Symptomatic polyhydramnios may be managed by serial amnioncenteses or by short-course maternal indomethacin if the problem is caused by excessive fetal urination. Treatment is indicated for acute maternal respiratory distress and threatened preterm labor or to provide time for the administration of corticosteroids to enhance fetal lung maturity.

Oligohydramnios is associated with congenital anomalies; intrauterine growth restriction; severe renal, bladder, or urethral anomalies; and drugs that interfere with fetal urination (see Table 95-4). Oligohydramnios becomes most evident after 20 wk of gestation, when fetal urination is the major source of amniotic fluid. Rupture of the membranes is the most common cause of oligohydramnios and must be ruled out if oligohydramnios is suspected, especially if a normal-sized...
The Fetus and the Neonatal Infant

Table 95-2  Maternal Conditions Affecting the Fetus or Neonate

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>EFFECT(S)</th>
<th>MECHANISM(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoantibody against folate receptors</td>
<td>Neural tube defects</td>
<td>Blockage of cellular uptake of folate</td>
</tr>
<tr>
<td>Cervical neoplasia</td>
<td>Preterm premature rupture of membranes</td>
<td>Associated with loop electrosurgical excision procedure or cone therapy</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>Preterm delivery, intrauterine fetal demise</td>
<td>Unknown, possibly hepatitis E</td>
</tr>
<tr>
<td>Cyanotic heart disease</td>
<td>Intrauterine growth restriction</td>
<td>Low fetal oxygen delivery</td>
</tr>
<tr>
<td>Diabetes mellitus: Mild</td>
<td>Large for gestational age, hypoglycemia</td>
<td>Fetal hyperglycemia—produces hyperinsulinemia; insulin promotes growth</td>
</tr>
<tr>
<td>Severe</td>
<td>Growth restriction</td>
<td>Vascular disease, placental insufficiency</td>
</tr>
<tr>
<td>Drug addiction</td>
<td>Intrauterine growth restriction, neonatal withdrawal</td>
<td>Direct drug effect plus poor diet</td>
</tr>
<tr>
<td>Endemic goiter</td>
<td>Hypothyroidism</td>
<td>Iodine deficiency</td>
</tr>
<tr>
<td>Graves disease (noninfectious)</td>
<td>Transient neonatal thyrotoxicosis</td>
<td>Placental immunoglobulin passage of thyroid-stimulating antibody</td>
</tr>
<tr>
<td>Herpes gestations (noninfectious)</td>
<td>Bullous rash, intrauterine fetal demise</td>
<td>Autoantibody similar to that in bullous pemphigoid</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Neonatal hypocalcemia</td>
<td>Maternal calcium crosses to fetus and suppresses fetal parathyroid gland</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Intrauterine growth restriction, intrauterine fetal demise</td>
<td>Placental insufficiency, fetal hypoxia</td>
</tr>
<tr>
<td>Idiopathic thrombocytopenic purpura</td>
<td>Thrombocytopenia</td>
<td>Nonspecific maternal platelet antibodies cross placenta</td>
</tr>
<tr>
<td>Isoimmune neutropenia or thrombocytopenia</td>
<td>Neutropenia or thrombocytopenia</td>
<td>Specific antifetus neutrophil or platelet antibody crosses placenta after sensitization of mother</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>Placental or fetal tumor</td>
<td>Metastasis</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Transient neonatal myasthenia</td>
<td>Immunoglobulin to acetylcholine receptor crosses placenta</td>
</tr>
<tr>
<td>Myotonic dystrophy</td>
<td>Neonatal myotonic dystrophy, congenital contractures, respiratory insufficiency</td>
<td>Genetic anticipation</td>
</tr>
<tr>
<td>Obesity</td>
<td>Macrosomia, hypoglycemia</td>
<td>Unknown</td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>Microcephaly, retardation</td>
<td>Elevated fetal phenylalanine values</td>
</tr>
<tr>
<td>Poor nutrition</td>
<td>Intrauterine growth restriction, adult insulin resistance</td>
<td>Reduced fetal nutrients, nutritional programming</td>
</tr>
<tr>
<td>Preeclampsia, eclampsia</td>
<td>Intrauterine growth restriction, thrombocytopenia, neutropenia, fetal demise</td>
<td>Uteroplacental insufficiency, fetal hypoxia, vasoconstriction</td>
</tr>
<tr>
<td>Renal transplantation</td>
<td>Intrauterine growth restriction</td>
<td>Uteroplacental insufficiency</td>
</tr>
<tr>
<td>Rhesus or other blood group sensitization</td>
<td>Fetal anemia, hypoalbuminemia, hydrops, neonatal jaundice</td>
<td>Antibody crosses placenta and is directed to fetal cells with antigen</td>
</tr>
<tr>
<td>Sickle cell anemia</td>
<td>Preterm birth, intrauterine growth restriction, stillbirth</td>
<td>Maternal sickling producing fetal hypoxia</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Congenital heart block, rash, anemia, thrombocytopenia, neutropenia</td>
<td>Antibody directed to fetal heart, red and white blood cells, and platelets</td>
</tr>
</tbody>
</table>

bladder is seen on fetal ultrasound. Oligohydramnios causes fetal compression abnormalities such as fetal distress, clubfoot, spadelike hands, and a flattened nasal bridge. The most serious complication of chronic oligohydramnios is pulmonary hypoplasia. The risk of umbilical cord compression during labor and delivery is increased in pregnancies complicated by oligohydramnios and may be alleviated by saline amnioinfusion. Prophylactic intrapartum amnioinfusion reduces the need for cesarean section and improves Apgar scores. Antenatal screening can be used to detect a number of disorders, including Down syndrome and other chromosomal abnormalities, neural tube defects and other structural anomalies, Tay-Sachs disease and other metabolic genetic diseases, hemoglobinopathies and other blood disorders, and cystic fibrosis. Screening methods include maternal blood tests, fetal ultrasound, and diagnostic tests on cells or fluid obtained by amniocentesis or chorionic villus sampling and by fetal blood or tissue sampling. Cell-free fetal DNA in maternal blood has higher sensitivity (>99%) and lower false-positive rates for trisomy 21 (Down syndrome) and other chromosomal abnormalities than a combination of maternal serum analytes and ultrasound. Second-trimester screening (15-18 wk) of maternal serum α-fetoprotein (MSAFP) values is used to screen for open neural tube defects. Approximately 90% of affected pregnancies can be detected by an elevated MSAFP value. Gastrochisis, omphalocele, congenital nephrosis, twins, and other abnormal conditions can also be identified.
Table 95-3  Maternal Infections Affecting the Fetus or Newborn

<table>
<thead>
<tr>
<th>INFECTION</th>
<th>MODE(S) OF TRANSMISSION</th>
<th>OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BACTERIA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group B streptococcus</td>
<td>Ascending cervical</td>
<td>Sepsis, pneumonia</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>Ascending cervical</td>
<td>Sepsis, pneumonia</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>Transplacental</td>
<td>Sepsis, pneumonia</td>
</tr>
<tr>
<td>Ureaplasma urealyticum</td>
<td>Ascending cervical</td>
<td>Sepsis, pneumonia</td>
</tr>
<tr>
<td>Mycoplasma hominis</td>
<td>Ascending cervical</td>
<td>Sepsis, pneumonia</td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td>Vaginal passage</td>
<td>Pneumonia, meningitis</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Transplacental, vaginal passage</td>
<td>Pneumonia, meningitis</td>
</tr>
<tr>
<td>Borrelia burgdorferi</td>
<td>Transplacental</td>
<td>Conagenic syphilis</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>Vaginal passage</td>
<td>Prematurity, fetal demise</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>Transplacental</td>
<td>Ophthalmia (conjunctivitis), sepsis, meningitis</td>
</tr>
<tr>
<td>Granulocytic ehrlichiosis</td>
<td>Transplacental</td>
<td>Prematurity, fetal demise, congenital tuberculosis</td>
</tr>
<tr>
<td><strong>VIRUS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rubella</td>
<td>Transplacental</td>
<td>Congenital rubella</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Transplacental, breast milk (rare)</td>
<td>Congenital cytomegalovirus or asymptomatic</td>
</tr>
<tr>
<td>HIV</td>
<td>Transplacental, vaginal passage, breast milk</td>
<td>Congenital acquired immunodeficiency syndrome</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Vaginal passage, transplacental, breast milk</td>
<td>Neonatal hepatitis, chronic hepatitis B surface antigen carrier state</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Transplacental</td>
<td>Uncommon, but neonatal hepatitis, chronic carrier state possible</td>
</tr>
<tr>
<td>Lymphocytic choriomeningitis</td>
<td>Transplacental</td>
<td>Fetal, neonatal death; hydrocephalus, chorioretinitis</td>
</tr>
<tr>
<td>Herpes simplex type 2 or 1</td>
<td>Transplacental</td>
<td>Congenital herpes simplex virus</td>
</tr>
<tr>
<td>Varicella-zoster</td>
<td>Vaginal passage, ascending</td>
<td>Neonatal encephalitis, disseminated viremia</td>
</tr>
<tr>
<td>Parvovirus</td>
<td>Transplacental</td>
<td>Congenital anomalies</td>
</tr>
<tr>
<td>Coxsackie B</td>
<td>Fecal-oral</td>
<td>Neonatal varicella</td>
</tr>
<tr>
<td>Poliomyelitis</td>
<td>Transplacental</td>
<td>Fetal anemia, hydrops</td>
</tr>
<tr>
<td>Epstein-Barr</td>
<td>Transplacental</td>
<td>Myocarditis, meningitis, hepatitis</td>
</tr>
<tr>
<td>Rubeola</td>
<td>Transplacental</td>
<td>Congenital poliomyelitis</td>
</tr>
<tr>
<td>West Nile</td>
<td>Transplacental</td>
<td>Anomalies(?)</td>
</tr>
<tr>
<td>Dengue virus</td>
<td>Transplacental</td>
<td>Abortion, fetal measles</td>
</tr>
<tr>
<td><strong>PARASITES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>Transplacental</td>
<td>Congenital toxoplasmosis or asymptomatic</td>
</tr>
<tr>
<td>Malaria</td>
<td>Transplacental</td>
<td>Abortion, prematurity, intrauterine growth restriction</td>
</tr>
<tr>
<td>Trypanosomiasis</td>
<td>Transplacental</td>
<td>Congenital Chagas disease</td>
</tr>
<tr>
<td>Hookworm</td>
<td>None</td>
<td>Maternal anemia, low birthweight</td>
</tr>
<tr>
<td><strong>FUNGII</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candida</td>
<td>Ascending, cervical</td>
<td>Sepsis, pneumonia, rash</td>
</tr>
<tr>
<td><strong>PRION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creutzfeldt-Jakob disease</td>
<td>Transplacental, colostrum</td>
<td>Hypothetical route, no long-term data</td>
</tr>
</tbody>
</table>

Low MSAFP is associated with incorrect gestational age estimates, trisomy 18 or 21, and intrauterine growth restriction.

A pregnancy should be considered high risk when the uterus is inappropriately large or small. A uterus large for the estimated stage of gestation suggests the presence of multiple fetuses, hydramnios, or an excessively large infant; an inappropriately small infant suggests oligohydramnios or poor intrauterine growth. PROM more than 24 hr before delivery carries a risk of fetal infection; it also increases the risk of premature birth. PROM at term usually results in the onset of labor within 48 hr but poses a risk of chorioamnionitis and umbilical cord compression. With PROM before 37 wk, there is a longer latency until labor starts, and its occurrence has the added risks of cord prolapse, oligohydramnios, abruptio placenta, fetal malposition; also, if membrane rupture is present for >7 days in a fetus during the 2nd trimester, pulmonary hypoplasia, uterine-induced deformations, and extremity contractures can develop. Prolonged and difficult labor increases the risk for mechanical and hypoxic damage. A tumultuous short labor with a precipitous delivery increases the risk of birth asphyxia and intracranial hemorrhage. Placental separation at any time before delivery and abnormal implantation or compression of the cord increase the possibility of brain damage from fetal hypoxia; brown or muddy amniotic fluid suggests that meconium has been passed, possibly during an episode of fetal hypoxia.

Although the safety of any type of delivery depends on the skill of the obstetrician, additional hazards accompany particular methods and result from the circumstances that dictated them. The risk of intracranial hemorrhage is greater in infants delivered by vacuum extraction or forceps than in those born unassisted in spontaneous vaginal deliveries. Neonatal deaths after mid-forceps delivery, breech extraction, and version are likely to be related to traumatic intracranial injury.

Infants born by cesarean section present problems possibly related to the unfavorable obstetric circumstance that necessitated the operation. In normal term pregnancies without any indication of fetal distress, cesarean section delivery carries a greater risk than delivery through the birth canal. Controversy exists regarding the safest type of delivery for a nondistressed, viable immature fetus, especially in a breech presentation; cesarean section may involve less risk than the “stress” of labor and the potentially hypoxic effects of uterine contractions during vaginal delivery. Term infants in breech position (≤3-4% of term births) that do not assume vertex position after external cephalic version attempts may also benefit from cesarean section.
**Table 95-4 Conditions Associated with Disorders of Amniotic Fluid Volume**

<table>
<thead>
<tr>
<th>Oligohydramnios</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amniotic fluid leak/rupture of membranes</td>
</tr>
<tr>
<td>Intruterine growth restriction</td>
</tr>
<tr>
<td>Fetal anomalies</td>
</tr>
<tr>
<td>Twin–twin transfusion (donor)</td>
</tr>
<tr>
<td>Renal agenesis (Potter syndrome)</td>
</tr>
<tr>
<td>Urethral atresia</td>
</tr>
<tr>
<td>Prune-belly syndrome</td>
</tr>
<tr>
<td>Pulmonary hypoplasia</td>
</tr>
<tr>
<td>Amnion nodosum</td>
</tr>
<tr>
<td>Indomethacin</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors or receptor antagonists</td>
</tr>
<tr>
<td>Intestinal pseudoobstruction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Polyhydramnios</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Congenital anomalies:</strong></td>
</tr>
<tr>
<td>Anencephaly</td>
</tr>
<tr>
<td>Hydrocephaly</td>
</tr>
<tr>
<td>Tracheoesophageal fistula</td>
</tr>
<tr>
<td>Duodenal atresia</td>
</tr>
<tr>
<td>Spina bifida</td>
</tr>
<tr>
<td>Cleft lip or palate</td>
</tr>
<tr>
<td>Cystic adenomatoid lung malformation</td>
</tr>
<tr>
<td>Diaphragmatic hernia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Syndromes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achondroplasia</td>
</tr>
<tr>
<td>Klippel-Feil</td>
</tr>
<tr>
<td>Trisomy 18</td>
</tr>
<tr>
<td>Trisomy 21</td>
</tr>
<tr>
<td>TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex)</td>
</tr>
<tr>
<td>Hydrops fetalis</td>
</tr>
<tr>
<td>Multiple congenital anomalies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Twin–twin transfusion (recipient)</td>
</tr>
<tr>
<td>Fetal anemia</td>
</tr>
<tr>
<td>Fetal heart failure</td>
</tr>
<tr>
<td>Polyuric renal disease</td>
</tr>
<tr>
<td>Neuromuscular diseases</td>
</tr>
<tr>
<td>Nonimmune hydrops</td>
</tr>
<tr>
<td>Chylothorax</td>
</tr>
<tr>
<td>Teratoma</td>
</tr>
<tr>
<td>Idiopathic</td>
</tr>
</tbody>
</table>

Although transient tachypnea is the most frequently associated problem with cesarean section, respiratory distress syndrome and persistent pulmonary hypertension may develop, particularly in infants born by cesarean section to women who are not in labor, in those with uncertain dates, and in those born to diabetic mothers or after asphyxia. A trial of labor after a previous low segment cesarean section may have benefits and harms but there are limited data to make firm recommendations. In women with more than one previous cesarean section, there is an increased risk of uterine rupture. An elective cesarean section should be delayed until ≥39 wk of gestation. Earlier delivery increases the risk to the newborns.

Anesthesia and analgesia affect the fetus as well as the mother; severe maternal hypoxemia secondary to hypoventilation or hypotension resulting from epidural anesthesia may lead to severe fetal hypoxia and shock. Skilled use of medication avoids severe fetal narcosis while securing the benefits of gentle and unhurried delivery. Even skilled administration may result in a mildly depressed infant whose crying and breathing may be delayed 1-2 min and who may be somewhat inactive for several hours.

*Bibliography is available at Expert Consult.*
Bibliography
Chapter 96
The Fetus
Waldemar A. Carlo and Namasivayam Ambalavanan

The major emphasis in fetal medicine involves (1) assessment of fetal growth and maturity, (2) evaluation of fetal well-being or distress, (3) assessment of the effects of maternal disease on the fetus, (4) evaluation of the effects of drugs administered to the mother on the fetus, and (5) identification and treatment of fetal disease or anomalies. Some aspects of human fetal growth and development are summarized in Chapter 8.

96.1 Fetal Growth and Maturity
Waldemar A. Carlo and Namasivayam Ambalavanan

Ultrasonography of the fetus, a common obstetric procedure, is both safe and reasonably accurate. Indications for antenatal ultrasonography include estimation of gestational age (unknown dates, discrepancy between uterine size and dates or suspected growth restriction), assessment of amniotic fluid volume, estimation of fetal weight, determination of the location of the placenta and the number and position of fetuses, and identification of congenital anomalies.

Fetal growth can be assessed by ultrasonography as early as 6-8 wk. The most accurate assessment of gestational age is by 1st-trimester ultrasound measurement of crown-rump length. The biparietal diameter is used to assess gestational age beginning in the 2nd trimester. Through 30 wk the biparietal diameter accurately estimates gestation to within ±10 days. Later in gestation, accuracy falls to ±3 wk. Methods used to assess gestational age closer to term include measurement of abdominal circumference and femoral length. If a single ultrasound examination is performed, the most information can be obtained with a scan at 18-20 wk, when both gestational age and fetal anatomy can be evaluated. Serial scans may be useful in assessing fetal growth. Two patterns of fetal growth restriction have been identified: continuous fetal growth 2 SD below the mean for gestational age or a normal fetal growth curve that abruptly slows or flattens later in gestation (Fig. 96-1).

Fetal maturity and dating are usually assessed by history (last menstrual period), physical examination, auscultation of fetal heart sounds at 16-18 wk, maternal perception of fetal movements at 18-20 wk, fundal height, and ultrasound (growth). Lung maturation may be estimated by determining the surfactant content of amniotic fluid (see Chapter 101.3).

Bibliography is available at Expert Consult.

96.2 Fetal Distress
Waldemar A. Carlo and Namasivayam Ambalavanan

Fetal compromise may occur during the antepartum or intrapartum period; it may be asymptomatic in the antenatal period. Antepartum fetal surveillance is warranted for women at increased risk for fetal death, including those with a history of stillbirth, intrauterine growth restriction (IUGR), oligohydramnios or polyhydramnios, multiple gestation, rhesus sensitization, hypertensive disorders, diabetes mellitus or other chronic maternal disease, decreased fetal movement, and postterm pregnancy. The predominant cause of antepartum fetal distress is uteroplacental insufficiency, which may manifest clinically as IUGR, fetal hypoxia, increased vascular resistance in fetal blood vessels (Figs. 96-2 and 96-3), and, when severe, mixed respiratory and
Bibliography


Chapter 96  The Fetus 807

Figure 96-1  A, Example of a “low-profile” growth retardation pattern in an uneventful pregnancy and labor. The baby cried at 1 min and hypoglycemia did not develop. Birthweight was below the 5th percentile for gestational age. B, Example of a “late-flattening” growth retardation pattern. The mother had a typical history of preeclampsia, and the infant had intrapartum fetal distress, a low Apgar score, and postnatal hypoglycemia. Birthweight was below the 5th percentile for gestational age. (From Campbell S: Fetal growth, Clin Obstet Gynecol 1:41–65, 1974.)

Figure 96-2  Normal Doppler velocity in sequential studies of fetal umbilical artery flow velocity waveforms from one normal pregnancy. Note the systolic peak flow with lower but constant heart flow during diastole. The systolic:diastolic ratio can be determined and, in normal pregnancies, is less than 3 after the 30th wk of gestation. The numbers indicate the weeks of gestation. (From Trudinger B: Doppler ultrasound assessment of blood flow. In Creasy RK, Resnik R, editors: Maternal-fetal medicine: principles and practice, ed 5, Philadelphia, 2004, WB Saunders.)

Figure 96-3  Abnormal umbilical artery Doppler in which the diastolic component shows flow in a reverse direction. This finding occurs in severe intrauterine hypoxia and intrauterine growth restriction. (From Trudinger C: Doppler ultrasound assessment of blood flow. In Creasy RK, Resnik R, editors: Maternal-fetal medicine: principles and practice, ed 5, Philadelphia, 2004, WB Saunders.)

metabolic (lactic) acidosis. The goals of antepartum fetal surveillance are to prevent intrauterine fetal demise, to prevent hypoxic brain injury, and to either prolong gestation in women at risk for preterm delivery when such prolongation is safe or deliver a fetus when it is in jeopardy. Table 96-1 lists methods for assessing fetal well-being.

The most commonly used noninvasive tests are the nonstress test (NST), the full and modified biophysical profile (BPP), and, less commonly, the contraction stress test (CST). The NST monitors the presence of fetal heart rate accelerations that follow fetal movement. A reactive (normal) NST result demonstrates 2 fetal heart rate accelerations of at least 15 beats/min lasting 15 sec. A nonreactive NST result suggests fetal compromise and requires further assessment with a CST or the BPP. A CST observes the fetal heart rate response to spontaneous, nipple-stimulated, or oxytocin-stimulated uterine contractions. Fetal compromise is suggested when the majority of contractions in 10 min are followed by late decelerations. A CST is relatively contraindicated in women with preterm premature rupture of membranes, a previous uterine scar from a classic cesarean section, multiple
gestations, incompetent cervix, and placenta previa. The goals of fetal monitoring are to prevent intrapartum fetal demise and hypoxic brain injury. Although the CST and NST have low false-negative rates, both have high false-positive rates. The full BPP assesses fetal breathing, body movement, tone, heart rate, and amniotic fluid volume, and it is used to improve the accurate and safe identification of fetal compromise (Table 96-2). A score of 2 is given for each observation present. A total score of 8-10 is reassuring; a score of 6 is equivocal, and retesting should be done in 12-24 hr; and a score of 4 or less warrants immediate evaluation and possible delivery. The BPP has good negative predictive value. The modified BPP consists of the combination of an ultrasound estimate of amniotic fluid volume (the amniotic fluid index) and the NST. When results of both are normal, fetal compromise is very unlikely. Signs of progressive compromise seen on Doppler ultrasonography include reduced, absent, or reversed diastolic waveform velocity in the fetal aorta or umbilical artery (see Fig. 96-3 and Table 96-1). High-risk fetuses often have combinations of abnormalities, such as oligohydramnios, reversed diastolic Doppler umbilical artery blood flow velocity, and a low BPP.

Fetal compromise during labor may be detected by monitoring the fetal heart rate, uterine pressure, and fetal scalp blood pH (Fig. 96-4). Continuous fetal heart rate monitoring detects abnormal cardiac patterns by instruments that compute the beat-to-beat fetal heart rate from a fetal electrocardiographic signal. Signals are derived from an electrode attached to the fetal presenting part, from an ultrasonic transducer placed on the maternal abdominal wall to detect continuous ultrasonic waves reflected from the contractions of the fetal heart, or from a phonotransducer placed on the mother's abdomen. Uterine contractions are simultaneously recorded from an amniotic fluid catheter and pressure transducer or from a tocoltransducer applied to the maternal abdominal wall overlying the uterus. Fetal heart rate patterns show various characteristics, some of which suggest fetal compromise. The baseline fetal heart rate is the average rate between uterine contractions, which gradually decreases from approximately 155 beats/min in early pregnancy to approximately 135 beats/min at term; the normal range at term is 110-160 beats/min. Tachycardia (>160 beats/min) is associated with early fetal hypoxia, maternal fever, maternal hyperthyroidism, maternal β-sympathomimetic drug or atropine therapy, fetal anemia, infection, and some fetal arrhythmias. The last do not generally occur with congenital heart disease and may resolve spontaneously at birth. Fetal bradycardia (<110 beats/min) may be normal (e.g., 105-110 beats/min) but may occur with fetal hypoxia, placental transfer of local anesthetic agents and β-adrenergic blocking agents, and, occasionally, heart block with or without congenital heart disease.

Normally, the baseline fetal heart rate is variable. Variability is classified as follows: absence of variability, if an amplitude change is undetectable; minimal variability if amplitude range is ≤5 beats/min...
Table 96-2 | Biophysical Profile Scoring: Technique and Interpretation

<table>
<thead>
<tr>
<th>BIOPHYSICAL VARIABLE</th>
<th>NORMAL SCORE (2)</th>
<th>ABNORMAL SCORE (0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal breathing movements (FBMs)</td>
<td>At least 1 episode of FBM of at least 30 sec duration in 30 min observation</td>
<td>Absence of FBM or no episode ≥30 sec in 30 min</td>
</tr>
<tr>
<td>Gross body movement</td>
<td>At least 3 discrete body/limb movements in 30 min (episodes of active continuous movement considered a single movement)</td>
<td>2 or fewer episodes of body/limb movements in 30 min</td>
</tr>
<tr>
<td>Fetal tone</td>
<td>At least 1 episode of active extension with return to flexion of fetal limb(s) or trunk Opening and closing of hand considered evidence of normal tone</td>
<td>Either slow extension with return to partial flexion or movement of limb in full extension or absence of fetal movement with the hand held in complete or partial deflection</td>
</tr>
<tr>
<td>Reactive fetal heart rate (FHR)</td>
<td>At least 2 episodes of FHR acceleration of ≥15 beats/min and at least 15 sec in duration associated with fetal movement in 30 min</td>
<td>Less than 2 episodes of acceleration of FHR or acceleration of &lt;15 beats/min in 30 min</td>
</tr>
<tr>
<td>Qualitative amniotic fluid (AF) volume*</td>
<td>At least 1 pocket of AF that measures at least 2 cm in 2 perpendicular planes</td>
<td>Either no AF pockets or a pocket &lt;2 cm in 2 perpendicular planes</td>
</tr>
</tbody>
</table>

*Modification of the criteria for reduced amniotic fluid from less than 1 cm to less than 2 cm would seem reasonable. Ultrasound is used for biophysical assessment of the fetus.


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Figure 96-4 | Patterns of periodic fetal heart rate deceleration. The tracing in A shows early deceleration occurring during the peak of uterine contractions as a result of pressure on the fetal head. B, Late deceleration caused by uteroplacental insufficiency. C, Variable deceleration as a result of umbilical cord compression. Arrows denote the time relationship between the onset of fetal heart rate changes and uterine contractions. (From Hon EH: An atlas of fetal heart rate patterns, New Haven, CT, 1968, Harty Press.)

(1 beats/min); moderate variability if amplitude range is 6-25 beats/min; marked variability if amplitude range is >25 beats/min. Variability may be decreased or lost with fetal hypoxemia or the placental transfer of drugs such as atropine, diazepam, promethazine, magnesium sulfate, and most sedative and narcotic agents. Prematurity, the sleep state, and fetal tachycardia may also diminish beat-to-beat variability.

Periodic accelerations or decelerations of the fetal heart rate in response to uterine contractions may also be monitored (see Fig. 96-4). An acceleration is an abrupt increase in fetal heart rate of ≥15 beats/
min in ≥15 sec. The presence of accelerations or moderate variability reliably predicts the absence of fetal metabolic acidemia. However, their absence does not reliably predict fetal acidemia or hypoxemia. Early deceleration associated with head compression is a repetitive pattern of gradual decrease and return of the fetal heart rate that is coincidental with the uterine contraction (Table 96-3). Variable deceleration (associated with cord compression) is characterized by variable shape, abrupt onset and occurrence with consecutive contractions, and return to baseline at or after the conclusion of the contraction. Late deceleration, associated with fetal hypoxemia, occurs repetitively after a uterine contraction is well established and persists into the interval following contractions. The late deceleration pattern is usually associated with maternal hypotension or excessive uterine activity, but it may be a response to any maternal, placental, umbilical cord, or fetal factor that limits effective oxygenation of the fetus. Reflex late decelerations with normal beat-to-beat variability are associated with chronic compensated fetal hypoxia, and they occur during uterine contractions that temporarily impede oxygen transport to the heart. Nonreflex late decelerations are more ominous and indicate severe hypoxic depression of myocardial function. Approximately 10–15% of term fetuses have terminal (just before delivery) fetal heart rate decelerations that are usually benign if they lasted <10 min prior to delivery. Neonates with longer terminal decelerations without recovery (persistent bradycardia) are associated with fetal acidosis and need neonatal ICU observation or treatment.

If late decelerations are unresponsive to oxygen supplementation, hydration, discontinuation of labor stimulation, and position changes, prompt delivery is indicated. A 3-tier system has been developed by a panel of experts for interpretation of fetal heart rate tracings (Table 96-4). Category I tracings are normal and are strongly predictive of normal fetal acid–base status at the time of the observation. Category II tracings are not predictive of abnormal fetal status, but there is insufficient evidence to categorize them as category I or III; further evaluation, surveillance, and reevaluation are indicated. Category III tracings are abnormal and predictive of abnormal fetal acid–base status at the time of observation. Category III tracings require prompt evaluation and efforts to expeditiously resolve the abnormal fetal heart rate as previously discussed for late decelerations.

Fetal scalp blood sampling during labor through a slightly dilated cervix may aid in confirming fetal distress suspected on the basis of variations in fetal heart rate or the presence of meconium in amniotic fluid.
The proper use of this technique may result in earlier delivery of depressed infants, who thus have a better chance of successful resuscitation, increased survival, and less morbidity. Alternatively, when continuous fetal heart rate monitoring or general clinical evaluation suggests that a fetus is at risk, a normal fetal scalp blood sample may help avert obstetric intervention.

Fetal scalp blood pH in normal labor decreases from approximately 7.33 early in labor to approximately 7.25 at the time of vaginal delivery; the base deficit is approximately 4.6 mEq/L. Changes in the buffer base may be particularly helpful in assessing fetal status, because they correspond to the accumulation of fetal lactic acid. A pH <7.25 suggests fetal distress, and a pH <7.20 is an indication for further assessment and intervention. Determination of the lactate concentration in fetal scalp blood is another tool for monitoring the condition of the fetus.

Umbilical cord blood samples obtained at the time of delivery are useful to document fetal acid-base status. Although the exact cord blood pH value that defines significant fetal acidemia is unknown, an umbilical artery pH <7.0 has been associated with greater need for resuscitation and a higher incidence of respiratory, gastrointestinal, cardiovascular, and neurologic complications. Nonetheless, in many cases, even when a low pH is detected, newborn infants are neurologically normal.

Intrapartum fetal pulse oximetry is another measure of fetal status. Even though initial data suggested that intrapartum fetal pulse oximetry could help identify fetuses with a non reassuring status, a large randomized controlled trial showed that intrapartum fetal pulse oximetry does not lead to a reduction in cesarean section rates or improvement in the condition of newborns at birth.

Bibliography is available at Expert Consult.

96.3 Maternal Disease and the Fetus

Waldemar A. Carlo and Namasivayam Ambalavanam

INFECTIONOUS DISEASES

See Table 95-3.

Almost any maternal infection with severe systemic manifestations may result in miscarriage, stillbirth, or premature labor. Whether these results are a consequence of infection of the fetus or are secondary to maternal illness is not always clear. Maternal hyperthermia may be associated with an increased incidence of congenital anomalies, including neural tube defects (NTDs). Regardless of the severity of the maternal infection, certain agents frequently infect the fetus and have serious sequelae. Fetuses of mothers infected with these agents are often small for gestational age and sometimes microcephalic. Some infections, such as rubella, may also produce congenital malformations if they occur during the period of organogenesis. Intrauterine infection/chorioamnionitis may be an important risk factor for cerebral white matter injury and subsequent cerebral palsy. Infec tions that affect maternal nutrition (e.g., hookworm) may also result in IUGR.

NONINFECTIONOUS DISEASES

See Table 95-2.

Maternal diabetes increases the risk for neonatal hypoglycemia, hypocalcemia, respiratory distress syndrome and other respiratory problems, polycthemia, macrosomia, myocardial dysfunction, jaundice, and congenital malformations (see Chapter 107.1). There is increased risk for incidence of uteroplacental insufficiency, polyhydramnios, and intrauterine death in poorly controlled diabetic mothers. Eclampsia–pre eclampsia of pregnancy, chronic hypertension, and chronic renal disease can result in IUGR, prematurity, and intrauterine death, all probably caused by diminished uteroplacental perfusion. Uncontrolled maternal hypothyroidism or hyperthyroidism is responsible for relative infertility, spontaneous abortion, premature labor, and fetal death. Hypothyroidism in pregnant women (even if mild or asymptomatic) can adversely affect neurodevelopment of the child. Maternal immunologic diseases such as idiopathic thrombocytopenic purpura, systemic lupus erythematosus, myasthenia gravis, and Graves disease, all of which are mediated by immunoglobulin G autoantibodies that can cross the placenta, frequently cause transient illness in the newborn. Maternal autoantibodies to the folate receptor are associated with NTDs, whereas maternal immunologic sensitization to paternal antigens may be associated with neonatal hemochromatosis. Untreated maternal phenylketonuria results in miscarriage, congenital cardiac malformations, and injury to the brain of a nonphenylketonuric heterozygotic fetus.

The use of medications or herbal remedies during pregnancy is potentially harmful to the fetus. Consumption of medications occurs during the majority of pregnancies. The average mother has taken 4 drugs other than vitamins or iron during pregnancy. Almost 40% of pregnant women receive a drug for which human safety during pregnancy has not been established (category C pregnancy risk; see later). Moreover, many women are exposed to potential reproductive toxins, such as occupational, environmental, or household chemicals, including solvents, pesticides, and hair products. The effects of drugs taken by the mother vary considerably, especially in relation to the time in pregnancy when they are taken and the fetal genotype for drug-metabolizing enzymes. Miscarriage or congenital malformations result from the maternal ingestion of teratogenic drugs during the period of organogenesis. Maternal medications taken later, particularly during the last few weeks of gestation or during labor, tend to affect the function of specific organs or enzyme systems, and they adversely affect the neonate rather than the fetus (Tables 96-5 and 96-6).

The effects of drugs may be evident immediately in the delivery room or later in the neonatal period, or they may be delayed even longer. The administration of diethylstilbestrol during pregnancy, for instance, increased the risk for vaginal adenocarcinoma in female offspring in the 2nd or 3rd decade of life.

Evidence has confirmed an interaction between genetic factors and susceptibility to certain drugs or environmental toxins. Phenytoin teratogenesis may be mediated by genetic differences in the enzymatic production of epoxide metabolites; specific genes may influence the adverse effects of benzene exposure during pregnancy. Polymorphisms of genes encoding enzymes that metabolize the polycyclic aromatic hydrocarbons in cigarette smoke influence the growth-restricting effects of smoking on the fetus.

Often the risk of controlling maternal disease must be balanced with the risk of possible complications in the fetus. The majority of women with epilepsy have normal fetuses. Nonetheless, several commonly used antiepileptic drugs are associated with congenital malformations. Infants exposed to valproic acid may have multiple anomalies, including NTDs, hypospadias, facial anomalies, cardiac anomalies, and limb defects. In addition, they have lower developmental index scores than unexposed infants and infants exposed to other commonly used antiepileptic drugs.

Methotrexate is used for medical termination of pregnancy; surviving exposed infants may be at higher risk for congenital anomalies, IUGR, hypotonia, and developmental delay.

Moderate or high alcohol intake (≥7 drinks per week or ≥3 drinks on multiple occasions) is a risk for fetal alcohol syndrome. The exposed fetuses are at risk for growth failure, central nervous system abnormalities, cognitive defects, and behavioral problems. Smoking during pregnancy is associated with IUGR and facial clefts.

In view of the limits of current knowledge about the fetal effects of maternal medication, drugs and herbal agents should not be prescribed...
Bibliography


Bibliography
during pregnancy without weighing of maternal need against the risk of fetal damage. All women should be specifically counseled to abstain from the use of alcohol, tobacco, and illicit drugs during pregnancy.

Bibliography is available at Expert Consult.

96.5 Teratogens

Waldemar A. Carlo and Namavigayam Ambalavan

When an infant or child has a congenital malformation or is developmentally delayed, the parents often wrongly blame themselves and attribute the child’s problems to events that occurred during pregnancy. Because benign infections occur and several nonteratogenic drugs are often taken during many pregnancies, the pediatrician must evaluate the presumed viral infections and the drugs ingested to help parents understand their child’s birth defect. The causes of approximately 40% of congenital malformations are unknown. Although only a relatively few agents are recognized to be teratogenic in humans (see Tables 96-5 and 96-6), new agents continue to be identified. Overall, only 10% of anomalies are due to recognizable teratogens (see Chapter 108). The time of exposure is usually during organogenesis at less than 60 days of gestation. Specific agents produce predictable lesions. Some agents have a dose or threshold effect; below the threshold, no alterations in growth, function, or structure occur. Genetic variables such as the presence of specific enzymes may metabolize a benign agent into a more toxic-teratogenic form (e.g., phenytoin conversion to its

### Table 96-5

<table>
<thead>
<tr>
<th>DRUG</th>
<th>EFFECT ON FETUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accutane (isotretinoin)</td>
<td>Facial-ear anomalies, heart disease, CNS anomalies</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Congenital cardiac, CNS, limb anomalies; IUGR; developmental delay; attention deficits; autism</td>
</tr>
<tr>
<td>Aminopterin</td>
<td>Abortion, malformations</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>Congenital heart disease, IUGR, withdrawal</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists</td>
<td>Oligohydramnios, IUGR, renal failure, Potter-like syndrome</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Abortion</td>
</tr>
<tr>
<td>Busulfan (Myleran)</td>
<td>Stunted growth; corneal opacities; cleft palate; hypoplasia of ovaries, thyroid, and parathyroids</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Spina bifida, possible neurodevelopmental delay</td>
</tr>
<tr>
<td>Carcinone</td>
<td>Scalp defects, choanal atresia, esophageal atresia, developmental delay</td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>Cerebral atrophy, microcephaly, seizures</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Deafness</td>
</tr>
<tr>
<td>Chorionic villus sampling</td>
<td>Probably no effect, possibly limb reduction</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>LBW for gestational age</td>
</tr>
<tr>
<td>Cocaine/crack</td>
<td>Microcephaly, LBW, IUGR, behavioral disturbances</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Multiple malformations</td>
</tr>
<tr>
<td>Danazol</td>
<td>Virilization</td>
</tr>
<tr>
<td>17α-Ethinyl testosterone (Progestoral)</td>
<td>Masculinization of female fetus</td>
</tr>
<tr>
<td>Hyperthermia</td>
<td>Spina bifida</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Possible increased risk of live vaccine associated disease in infant; neutropenia</td>
</tr>
<tr>
<td>Lithium</td>
<td>Ebstein anomaly, macrosomia</td>
</tr>
<tr>
<td>Lopinavir-ritonavir</td>
<td>Transient adrenal dysfunction</td>
</tr>
<tr>
<td>6-Mercaptopurine</td>
<td>Abortion</td>
</tr>
<tr>
<td>Methyl mercury</td>
<td>Minamata disease, microcephaly, deafness, blindness, mental retardation</td>
</tr>
<tr>
<td>Methyltestosterone</td>
<td>Masculinization of female fetus</td>
</tr>
<tr>
<td>Misoprostol</td>
<td>Arthrogryposis, cranial neuropathies (Möbius syndrome), equinovarus</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>Craniofacial, limb, cardiovascular, CNS anomalies</td>
</tr>
<tr>
<td>Norethindrone</td>
<td>Masculinization of female fetus</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>Cutis laxa syndrome</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Congenital anomalies, IUGR, neuroblastoma, bleeding (vitamin K deficiency)</td>
</tr>
<tr>
<td>Polychlorinated biphenyls</td>
<td>Skin discoloration—thickening, desquamation, LBW, acne, developmental delay</td>
</tr>
<tr>
<td>Prednisone</td>
<td>Oral clefts</td>
</tr>
</tbody>
</table>
Bibliography


### Table 96-5 | Agents Acting on Pregnant Women That May Adversely Affect the Structure or Function of the Fetus and Newborn—cont’d

<table>
<thead>
<tr>
<th>DRUG</th>
<th>EFFECT ON FETUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone</td>
<td>Masculinization of female fetus</td>
</tr>
<tr>
<td>Quinine</td>
<td>Abortion, thrombocytopenia, deafness</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>Small increased risk of congenital anomalies, persistent pulmonary hypertension of newborn</td>
</tr>
<tr>
<td>Statins</td>
<td>IUGR, limb deficiencies, VACTERAL</td>
</tr>
<tr>
<td>Stilbestrol (diethylstilbestrol [DES])</td>
<td>Vaginal adenocarcinoma in adolescence</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Deafness</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Retarded skeletal growth, pigmentation of teeth, hypoplasia of enamel, cataract, limb malformations</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Phocomelia, deafness, other malformations</td>
</tr>
<tr>
<td>Toluene (solvent abuse)</td>
<td>Craniofacial abnormalities, prematurity, withdrawal symptoms, hypertonia</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Cleft lip</td>
</tr>
<tr>
<td>Trimethadione and paramethadione</td>
<td>Abortion, multiple malformations, mental retardation</td>
</tr>
<tr>
<td>Valproate</td>
<td>CNS (spina bifida), facial and cardiac anomalies, limb defects, impaired neurologic function, autism spectrum disorder</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Supravalvular aortic stenosis, hypercalcemia</td>
</tr>
<tr>
<td>Warfarin (Coumadin)</td>
<td>Fetal bleeding and death, hypoplastic nasal structures</td>
</tr>
</tbody>
</table>

CNS, central nervous system; IUGR, intrauterine growth restriction; LBW, low birthweight. VACTERAL, vertebral, anal, cardiac, tracheoesophageal fistula, renal, arterial, limb.

### Table 96-6 | Agents Acting on Pregnant Women That May Adversely Affect the Newborn Infant*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Effect on Newborn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>IUGR, hypotension, bradycardia</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Bradycardia, hypothyroidism</td>
</tr>
<tr>
<td>Anesthetic agents (volatile)</td>
<td>CNS depression</td>
</tr>
<tr>
<td>Adrenal corticosteroids</td>
<td>Adrenocortical failure (rare)</td>
</tr>
<tr>
<td>Ammonium chloride</td>
<td>Acidosis (clinically inapparent)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Neonatal bleeding, prolonged gestation</td>
</tr>
<tr>
<td>Atenolol</td>
<td>IUGR, hypoglycemia</td>
</tr>
<tr>
<td>Baclofen</td>
<td>Withdrawal</td>
</tr>
<tr>
<td>Blue cohosh herbal tea</td>
<td>Neonatal heart failure</td>
</tr>
<tr>
<td>Bromides</td>
<td>Rash, CNS depression, IUGR</td>
</tr>
<tr>
<td>Captopril, enalapril</td>
<td>Transient anuric renal failure, oligohydramnios</td>
</tr>
<tr>
<td>Caudal-paracervical anesthesia with mepipvacaine</td>
<td>Accidental introduction of anesthetic into scalp of baby—bradypnea, apnea, bradycardia, convulsions</td>
</tr>
<tr>
<td>Cholinergic agents (edrophonium, pyridostigmine)</td>
<td>Transient muscle weakness</td>
</tr>
<tr>
<td>CNS depressants (narcotics, barbiturates, benzodiazepines) during labor</td>
<td>CNS depression, hypotonia</td>
</tr>
<tr>
<td>Cephalothin</td>
<td>Positive direct Coombs test reaction</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Pneumothorax, leukomalacia</td>
</tr>
<tr>
<td>Fluoxetine and other SSRIs</td>
<td>Transient neonatal withdrawal, hypertonicity, minor anomalies, preterm birth, prolonged QT interval</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Withdrawal</td>
</tr>
<tr>
<td>Hexamethonium bromide</td>
<td>Paralytic ileus</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Oligohydramnios, pulmonary hypertension</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Withdrawal</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Oliguria, oligohydramnios, intestinal perforation, pulmonary hypertension</td>
</tr>
<tr>
<td>Intravenous fluids during labor (e.g., salt-free solutions)</td>
<td>Electrolyte disturbances, hyponatremia, hypoglycemia</td>
</tr>
<tr>
<td>Iodide (radioactive)</td>
<td>Goiter</td>
</tr>
<tr>
<td>Iodides</td>
<td>Goiter</td>
</tr>
<tr>
<td>Lead</td>
<td>Reduced intellectual function</td>
</tr>
<tr>
<td>Magnesium sulfate</td>
<td>Respiratory depression, meconium plug, hypotonia</td>
</tr>
<tr>
<td>Methimazole</td>
<td>Goiter, hypothyroidism</td>
</tr>
<tr>
<td>Morphine and its derivatives (addiction)</td>
<td>Withdrawal symptoms (poor feeding, vomiting, diarrhea, restlessness, yawning and stretching, dyspnea and cyanosis, fever and sweating, pallor, tremors, convulsions)</td>
</tr>
<tr>
<td>Naphthylamine</td>
<td>Hemolytic anemia (in G6PD-deficient infants)</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Hemolytic anemia (in G6PD-deficient infants)</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>Hyperbilirubinemia, hyponatremia</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Bleeding diathesis (vitamin K deficiency), possible long-term reduction in IQ, sedation</td>
</tr>
<tr>
<td>Primaquine</td>
<td>Hemolytic anemia (in G6PD-deficient infants)</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Hypoglycemia, bradycardia, apnea</td>
</tr>
</tbody>
</table>

Continued
Radiation

The U.S. Food and Drug Administration (FDA) classifies drugs into 5 pregnancy risk categories. **Category A** drugs pose no risk on the basis of evidence from controlled human studies. For **category B** drugs, either no risk has been shown in animal studies but no adequate studies in humans or some risk has been shown in animal studies but these results are not confirmed by human studies. For **category C** drugs, either definite risk has been shown in animal studies but no adequate human studies have been performed or no data is available from either animal or human studies. **Category D** includes drugs with some risk but with a benefit that may exceed that risk for the treated life-threatening condition, such as streptomyacin for tuberculosis. **Category X** is for drugs that are contraindicated in pregnancy on the basis of animal and human evidence and for which the risk exceeds the benefits.

The specific mechanism of action is known or postulated for very few teratogens. Warfarin, an anticoagulant because it is a vitamin K antagonist, prevents the carboxylation of γ-carboxyglutamic acid, which is a component of osteocalcin and other vitamin K–dependent bone proteins. The teratogenic effect of warfarin on developing cartilage, especially nasal cartilage, appears to be avoided if the pregnant woman's anticoagulation treatment is switched from warfarin to heparin for the period between weeks 6 and 12 of gestation. Hypothyroidism in the fetus may be caused by the maternal ingestion of an excessive amount of iodides or propylthiouracil; each interferes with the conversion of inorganic to organic iodides. Phenytoin may be teratogenic because of the accumulation of a metabolite as a result of the conversion of inorganic to organic iodides. Propylthiouracil—goiter, hypothyroidism

Pyridoxine—seizures
Reserpine—drowsiness, nasal congestion, poor temperature stability
Sulfonamides—interfere with protein binding of bilirubin; kernicterus at low levels of serum bilirubin, hemolytic with G6PD deficiency
Sulfonylurea agents—refractory hypoglycemia
Sympathomimetic (tocolytic β-agonist) agents—tachycardia
Thiazides—neonatal thrombocytopenia (rare)
Tumor necrosis factor blocking agents—neutropenia
Valproate—developmental delay
Zolpidem (Ambien)—low birthweight

*See also Table 96-5.

CNS, central nervous system; G6PD, glucose-6-phosphate dehydrogenase; IUGR, intrauterine growth restriction; SSRI, selective serotonin reuptake inhibitor.

**96.7 Intrauterine Diagnosis of Fetal Disease**

Waldemar A. Carlo and Namasivayam Ambalavanan

See Table 96-1 and Chapter 96.2.

Diagnostic procedures are used to identify fetal diseases when abortion is being considered, when direct fetal treatment is possible, or when a decision is made to deliver a viable but premature infant to avoid intrauterine fetal demise. Fetal assessment is also indicated in a broader context when the family, medical, or reproductive history of the mother suggests the presence of a high-risk pregnancy or a high-risk fetus (see Chapters 95 and 96.3). Various methods are used for identifying fetal disease (see Table 96-1). Fetal ultrasonographic imaging may detect fetal growth abnormalities (by biometric measurements of biparietal diameter, femoral length, or head or abdominal circumference) or fetal malformations (Fig. 96-5). Although 89% of fetuses whose biparietal diameter is 9.5 cm or more are at least in the 37th wk of gestation, the lungs of these fetuses may not be mature. Serial determinations of growth velocity and the head-to-abdomen circumference ratio enhance the ability to detect IUGR. Real-time ultrasonography may identify placental abnormalities (abruptio placenta, placenta previa) and fetal anomalies such as hydrocephalus, NTDs, duodenal atresia, diaphragmatic hernia, renal agenesis, bladder outlet obstruction, congenital heart disease, limb abnormalities, sacrococcygeal teratoma, cystic hygroma, omphalocele, gastrochisis, and hydrops (Table 96-7). Real-time ultrasonography also facilitates performance of cordocentesis and the BPP by imaging fetal breathing, body movements, tone, and amniotic fluid volume (see Table 96-2). Doppler velocimetry...
Bibliography
Bibliography
assesses fetal arterial blood flow (vascular resistance) (see Figs. 96-2 and 96-3). Radiographic examination of the fetus has been replaced by real-time ultrasonography, MRI, and fetoscopy.

Amniocentesis, the transabdominal withdrawal of amniotic fluid during pregnancy for diagnostic purposes (see Table 96-1), is frequently performed to determine the timing of delivery of fetuses with erythroblastosis fetalis or the need for fetal transfusion. It is also done for genetic indications, usually between the 15th and 16th wk of gestation, with results available within 1-2 wk. The most common indication for genetic amniocentesis is advanced maternal age (the risk for chromosome abnormality at age 21 yr is 1:526, vs. 1:8 at age 49 yr). The amniotic fluid may be directly analyzed for amino acids, enzymes, hormones, and abnormal metabolic products, and amniotic fluid cells may be cultivated to permit detailed cytologic analysis for prenatal detection of chromosomal abnormalities and DNA-gene or enzymatic analysis for the detection of inborn metabolic errors. Analysis of amniotic fluid may also help in identifying NTDs (elevation of α-fetoprotein), adrenogenital syndrome (elevation of 17-ketosteroids and pregnanetriol), and thyroid dysfunction. Chorionic villus biopsy (transvaginal or transabdominal) performed in the 1st trimester also provides fetal cells but may pose a slightly increased risk for fetal loss and limb reduction defects. Fetal DNA in maternal plasma and fetal cells circulating in maternal blood are potential noninvasive sources of material for prenatal diagnosis. This technology may eliminate the need for amniocentesis or chorionic villus sampling.

**Figure 96-5 Assessment of fetal anatomy.** A, Overall view of the uterus at 24 wk showing a longitudinal section of the fetus and an anterior placenta. B, Transverse section at the level of the lateral ventricle at 18 wk showing (on the right) prominent anterior horns of the lateral ventricles on either side of the midline echo of the falx. C, Cross-section of the umbilical cord showing that the lumen of the umbilical vein is much wider than that of the 2 umbilical arteries. D, Four-chambered view of the heart at 18 wk with equal-sized atria. E(i), Normal male genitals near term. E(ii), Hydrocele outlining a testicle within the scrotum projecting into a normal-size pocket of amniotic fluid at 38 wk. Approximately 2% of male infants after birth have clinical evidence of a hydrocele that is often bilateral, not to be confused with subcutaneous edema occurring during vaginal breech birth. F, Section of a thigh near term showing thick subcutaneous tissue (4.6 mm between markers) above the femur of a fetus with macromelia. G, Fetal face viewed from below, showing (from right to left) the nose, alveolar margin, and chin at 20 wk. (From Special investigative procedures. In Beischer NA, Mackay EV, Colditz PB, editors: Obstetrics and the newborn, ed 3, Philadelphia, 1997, WB Saunders.)
### Table 96-7 | Significance of Fetal Ultrasonographic Anatomic Findings

<table>
<thead>
<tr>
<th>PRENATAL OBSERVATION</th>
<th>DEFINITION</th>
<th>DIFFERENTIAL DIAGNOSIS</th>
<th>SIGNIFICANCE</th>
<th>POSTNATAL EVALUATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilated cerebral ventricles</td>
<td>Ventriculomegaly ≥10 mm</td>
<td>Hydrocephalus</td>
<td>Transient isolated ventriculomegaly is common and usually benign</td>
<td>Serial head US or CT Evaluate for extracranial anomalies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hydranencephalous Dandy-Walker cyst</td>
<td>Persistent or progressive ventriculomegaly more worrisome</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Agenesis of corpus callosum</td>
<td>Identify associated cranial and extracranial anomalies</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bilateral ventriculomegaly increases risk of developmental delay</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unilateral ventriculomegaly may be normal variant</td>
<td></td>
</tr>
<tr>
<td>Choroid plexus cysts</td>
<td>Size ~10 mm: unilateral or bilateral</td>
<td>Abnormal karyotype (trisomy 18, 21)</td>
<td>Often isolated, benign; resolves by 24-28 wk</td>
<td>Head US or CT Examine for extracranial anomalies; karyotype if indicated</td>
</tr>
<tr>
<td></td>
<td>1-3% incidence</td>
<td>Aneuploidy risk 1:100 if isolated. Risk 1:3 with other anomalies. Risk ↑ if large, complex, or bilateral cysts or advanced maternal age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuchal pad thickening</td>
<td>≥6 mm at 15-20 wk</td>
<td>Cystic hygroma trisomy 21, 18 Turner syndrome (XO) Nonchromosomal syndromes Normal (~25%)</td>
<td>&lt;50% of affected fetuses have chromosome abnormalities Amniocentesis for karyotype needed</td>
<td>Evaluate for multiple organ malformations; karyotype if indicated</td>
</tr>
<tr>
<td>Dilated renal pelvis</td>
<td>Pyelectasis ≥5 to 10 mm</td>
<td>Uteropelvic junction obstruction Vescicoureteral reflux Posterior ureteral valves Entopic ureteroceles Large-volume nonobstruction</td>
<td>Often “physiologic” and transient reflux is common If dilation is &gt;10 mm or associated with caliectasis, pathologic cause should be considered If large bladder present, posterior urethral valves and megacystic-megaduodenum syndrome should be considered</td>
<td>Repeat ultrasonography on day 5 and at 1 mo; voiding cystoureterogram prophylactic antibiotics</td>
</tr>
<tr>
<td>Echogenic bowel</td>
<td>0.6% incidence</td>
<td>CF, meconium peritonitis, trisomy 21 or 18, other chromosomal abnormalities cytomegalovirus, toxoplasmosis, GI obstruction</td>
<td>Often normal (65%) 10% of affected fetuses have CF; 1.5% have aneuploidy</td>
<td>Sweat chloride and DNA testing Karyotype Surgery for obstruction Evaluation for TORCH (toxoplasmosis, other agents, rubella, CMV, herpes simplex) syndrome</td>
</tr>
<tr>
<td>Stomach appearance</td>
<td>Small or absent or with double bubble</td>
<td>Upper GI obstruction (esophageal atresia) Double bubble signifies duodenal atresia Abnormal karyotype Polyhydramnios Stomach in chest signifies diaphragmatic hernia</td>
<td>Must also consider neurologic disorders that reduce swallowing Over 30% with double bubble have trisomy 21</td>
<td>Chromosomes, kidney, ureter, and bladder radiograph if indicated, upper GI series, neurologic evaluation</td>
</tr>
</tbody>
</table>

**Notes:**
- **CF**: cystic fibrosis
- **CMV**: cytomegalovirus
- **GI**: gastrointestinal
- **US**: ultrasound

The best available chemical indices of fetal maturity are provided by determination of amniotic fluid creatinine and lecithin levels, which reflect the maturity of the fetal kidneys and lungs, respectively. Lecithin is produced in the lungs by type II alveolar cells and eventually reaches the amniotic fluid via the effluent from the trachea. Until the middle of the 3rd trimester, its concentration nearly equals that of sphingomyelin; thereafter, the sphingomyelin concentration remains constant in amniotic fluid while the lecithin concentration increases. By 35 wk, the lecithin: sphingomyelin (L:S) ratio averages about 2:1, indicative of lung maturity.

Earlier lung maturation may occur in the presence of severe premature separation of the placenta, premature rupture of the fetal membranes, narcotic addiction, or maternal hypertensive and renal vascular disease. A delay in pulmonary maturation may be associated with hydrops fetalis or maternal diabetes without vascular disease. The likelihood of hyaline membrane disease is greatly reduced with L:S ratios of 2:1 or more, although hypoxia, acidosis, and hypothermia may increase the risk despite this “mature” L:S ratio. Maternal and fetal blood have an L:S ratio of about 1:4; thus, contamination will not alter the significance of a ratio of 2:1 or more. Meconium contamination,
sample storage, and sample centrifugation may reduce the reliability of the L:S ratio.

Saturated phosphatidylcholine or phosphatidylglycerol concentrations in amniotic fluid may be more specific and sensitive predictors of pulmonary maturity, especially in high-risk pregnancies such as those occurring in women with diabetes (see Chapters 95 and 107.1). Amniocentesis can be carried out with little discomfort to the mother, but even in experienced hands, the procedure entails some small risk, such as direct damage to the fetus, placental puncture and bleeding with secondary damage to the fetus, stimulation of uterine contraction and premature labor, amnionitis, and maternal sensitization to fetal blood. The earlier in gestation that amniocentesis is done, the greater the risk to the fetus. Using ultrasound for placental and fetal localization can reduce the risk of complications. The procedure should be limited to cases in which the potential benefits of the findings will outweigh the risk.

**Cordocentesis**, or percutaneous umbilical blood sampling, is used to diagnose fetal hematologic abnormalities, genetic disorders, infections, and fetal acidosis (see Table 96-1). Under direct ultrasonographic visualization, a long needle is passed into the umbilical vein at its entrance to the placenta or fetal abdominal wall. Umbilical blood may be withdrawn to determine fetal hemoglobin, platelet concentration, lymphocyte DNA, the presence of infection, or PaO₂, pH, Pco₂, and lactate levels. Transfusion or administration of drugs can be performed through the umbilical vein (Table 96-8). Serum screening is offered to pregnant women at midgestation to evaluate the risk for Down syndrome (trisomy 21) and congenital malformations known to cause elevations of various markers, including abdominal wall and NTDs. A combination of these biochemical markers (including α-fetoprotein, inhibin A, estriol, pregnancy-associated plasma protein A, and β-HCG [human chorionic gonadotropin]) and ultrasound increases the positive

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>POSSIBLE TREATMENT</th>
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<tbody>
<tr>
<td><strong>HEMATOLOGIC</strong></td>
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<tr>
<td>Anemia with hydrops (erythroblastosis fetalis)</td>
<td>Umbilical vein packed red blood cell transfusion</td>
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<tr>
<td>Thalassemia</td>
<td>Fetal stem cell transplantation</td>
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<td>Isoimmune thrombocytopenia</td>
<td>Umbilical vein platelet transfusion, maternal IVIG</td>
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<tr>
<td>Autoimmune thrombocytopenia (ITP)</td>
<td>Maternal steroids and IVIG</td>
</tr>
<tr>
<td>Chronic granulomatous disease</td>
<td>Fetal stem cell transplantation</td>
</tr>
<tr>
<td><strong>METABOLIC-ENDOCRINE</strong></td>
<td>Phenylalanine restriction</td>
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<tr>
<td>Maternal phenylketonuria (PKU)</td>
<td>Galactose-free diet (?)</td>
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<tr>
<td>Fetal galaclosemia</td>
<td>Biotin if responsive</td>
</tr>
<tr>
<td>Multiple carboxylase deficiency</td>
<td>Vitamin B₁₂ if responsive</td>
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<tr>
<td>Methylmalonic acidemia</td>
<td>Dexamethasone</td>
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<tr>
<td>21-Hydroxylase deficiency</td>
<td>Tight insulin control during pregnancy, labor, and delivery</td>
</tr>
<tr>
<td>Maternal diabetes mellitus</td>
<td>Maternal hyperthyroidism—intra-amniotic thyroxine</td>
</tr>
<tr>
<td>Fetal goiter</td>
<td>Fetal hypothyroidism—intra-amniotic thyroxine</td>
</tr>
<tr>
<td><strong>FETAL DISTRESS</strong></td>
<td>Maternal indomethacin may prevent nephrocalcinosis and postnatal sodium losses</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>Maternal oxygen, position</td>
</tr>
<tr>
<td>Intrauterine growth restriction</td>
<td>Maternal oxygen, position, improve macronutrients and micronutrients if deficient</td>
</tr>
<tr>
<td>Oligohydramnios, premature rupture of membranes with variable deceleration</td>
<td>Amnioinfusion (antepartum and intrapartum)</td>
</tr>
<tr>
<td>Polyhydramnios</td>
<td>Amnioinfusion (serial), indomethacin (if from increased urine output) if indicated</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>Maternal digoxin, flecainide, procanamide, amiodarone, quinidine</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>Maternal aspirin, prednisone</td>
</tr>
<tr>
<td>Meconium-stained fluid</td>
<td>Amnioinfusion</td>
</tr>
<tr>
<td>Congenital heart block</td>
<td>Dexamethasone, pacemaker (with hypdrops)</td>
</tr>
<tr>
<td>Premature labor</td>
<td>Magnesium sulfate, antibiotics sympathomimetics, indomethacin</td>
</tr>
<tr>
<td><strong>REPRODUCTIVE</strong></td>
<td>Betamethasone</td>
</tr>
<tr>
<td>Pulmonary immaturity</td>
<td>Thoracentesis, pleuroamniotic shunt</td>
</tr>
<tr>
<td>Bilateral chylothorax—pleural effusions</td>
<td><strong>CONGENITAL ABNORMALITIES</strong></td>
</tr>
<tr>
<td>Neural tube defects</td>
<td>Folate, vitamins (prevention); fetal surgery †</td>
</tr>
<tr>
<td>Posterior urethral valves, urethral atresia (lower urinary tract obstruction)</td>
<td>Percutaneous vesicoamniotic shunt</td>
</tr>
<tr>
<td>Cystic adenosomatous malformation (with hydrops)</td>
<td>Pleuroamniotic shunt or resection ‡</td>
</tr>
<tr>
<td>Fetal neck masses</td>
<td>Secure an airway with EXIT procedure ‡</td>
</tr>
<tr>
<td><strong>INFECTIOUS DISEASE</strong></td>
<td>Amoxicillin, penicillin</td>
</tr>
<tr>
<td>Group B streptococcus colonization</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>Spiramycin, pyrimethamine, sulfadiazine, and folic acid</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>Penicillin</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Antituberculous drugs</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Penicillin, ceftriaxone</td>
</tr>
<tr>
<td>Lyme disease</td>
<td>Intrauterine red blood cell transfusion for hydrops, severe anemia</td>
</tr>
<tr>
<td>Parvovirus</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td>Maternal and neonatal antiretroviral therapy (see Chapter 276)</td>
</tr>
<tr>
<td>HIV-AIDS</td>
<td>Ganciclovir by umbilical vein</td>
</tr>
</tbody>
</table>
| Cytomegalovirus |Continued
predictive value of these screening tests. Nonetheless fetal karyotyping by analysis of fetal DNA in maternal plasma is another accurate method to diagnose trisomy 21. Additionally, families with a known genetic syndrome may be offered prenatal genetic testing from amniotic fluid or amniocytes obtained via amniocentesis or chorionic villus sampling.

Bibliography is available at Expert Consult.

### 96.8 Treatment and Prevention of Fetal Disease

*Waldemar A. Carlo and Namasiyavam Ambalavanan*

Management of a fetal disease depends on coordinated advances in diagnostic accuracy and knowledge of the disease's natural history; an understanding of fetal nutrition, pharmacology, immunology, and pathophysiology; the availability of specific active drugs that cross the placenta; and therapeutic procedures. Progress in providing specific treatments for accurately diagnosed diseases has improved with the advent of real-time ultrasonography and cordocentesis (see Tables 96-1 and 96-8).

The incidence of sensitization of Rh-negative women by Rh-positive fetuses has been reduced by prophylactic administration of Rh(D) immunoglobulin to mothers early in pregnancy and after each delivery or abortion, thus reducing the frequency of hemolytic disease in their subsequent offspring. Fetal erythroblastosis (see Chapter 103.2) may be accurately diagnosed by amniotic fluid analysis and treated with intrauterine intraperitoneal or, more often, intraumbilical vein transfusions of packed Rh-negative blood cells to maintain the fetus until it is mature enough to have a reasonable chance of survival.

**Fetal hypoxia or distress** may be diagnosed with moderate success. Treatment, however, remains limited to supplying the mother with high concentrations of oxygen, positioning the uterus to avoid vascular compression, and initiating operative delivery before severe fetal injury occurs.

**Pharmacologic** approaches to fetal immaturity (e.g., administration of steroids to the mother to accelerate fetal lung maturation and decrease the incidence of respiratory distress syndrome [Chapter 101.3] in prematurely delivered infants) are successful. Inhibiting labor with tocolytic agents is unfortunately not successful in most patients with premature labor. Management of definitively diagnosed fetal genetic disease or congenital anomalies consists of parental counseling or abortion; rarely, high-dose vitamin therapy for a responsive inborn error of metabolism (biotin-dependent disorders) or fetal transfusion (with red blood cells or platelets) may be indicated. Fetal surgery (see Table 96-8) remains an largely experimental approach to therapy and is available only in a few highly specialized perinatal centers. The nature of the defect and its consequences, as well as ethical implications for the fetus and the parents, must be considered. In a randomized controlled trial, fetal surgery for myelomeningocele improved neurological function (mental and motor development) and decreased the need for shunts by 50% but increased the prematurity rate.

Folic acid supplementation decreases the incidence and recurrence of (NTDs). Because the neural tube closes within the 1st 28 days of conception, periconceptional supplementation is needed for prevention. It is recommended that women without a prior history of a NTD ingest 400 µg/day of folic acid throughout their reproductive years. Women with a history of a prior pregnancy complicated by an NTD or a 1st-degree relative with an NTD should have preconceptional counseling and should ingest 4 mg/day of supplemental folic acid beginning at least 1 mo before conception. Fortification of cereal grain flour with folic acid is established policy in the United States and some other countries. The optimal concentration of folic acid in enriched grains is somewhat controversial. The incidence of NTD in the United States and other countries has decreased significantly since these public health initiatives were implemented. Use of some antiepileptic drugs (valproate, carbamazepine) during pregnancy is associated with an increased risk of NTD. Women taking these medications should ingest 1-5 mg of folic acid/day in the preconception period.

Bibliography is available at Expert Consult.

### Table 96-8 Fetal Therapy

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>POSSIBLE TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTHER</td>
<td></td>
</tr>
<tr>
<td>Nonimmune hydrops (anemia)</td>
<td>Umbilical vein packed red blood cell transfusion</td>
</tr>
<tr>
<td>Narcotic abstinence (withdrawal)</td>
<td>Maternal low-dose methadone</td>
</tr>
<tr>
<td>Severe combined immunodeficiency disease</td>
<td>Fetal stem cell transplantation</td>
</tr>
<tr>
<td>Sacrococcygeal teratoma (with hydrops)</td>
<td>In utero resection or catheter directed vessel obliteration</td>
</tr>
<tr>
<td>Twin-twin transfusion syndrome</td>
<td>Repeated amniocentesis, yttrium-aluminum-garnet (YAG) laser photoocoagulation of shared vessels</td>
</tr>
<tr>
<td>Twin reversed arterial perfusion (TRAP) syndrome</td>
<td>Digoxin, indomethacin, cord occlusion</td>
</tr>
<tr>
<td>Multifetal gestation</td>
<td>Selective reduction</td>
</tr>
<tr>
<td>Neonatal hemochromatosis</td>
<td>Maternal IVIG</td>
</tr>
</tbody>
</table>

*Drug of choice (may require percutaneous umbilical cord sampling and umbilical vein administration if hydrops is present). Most drug therapy is given to the mother, with subsequent placental passage to the fetus.

†Detailed fetal ultrasonography is needed to detect other anomalies; karyotype is also indicated.

‡EXIT permits surgery and other procedures.

EXIT, ex utero intrapartum treatment; IVIG, intravenous immunoglobulin; (?), possible but not proved efficacy.
Bibliography


Neonates at risk should be identified as early as possible prenatally or after birth to decrease neonatal morbidity and mortality (see Chapter 93). The term *high-risk infant* designates an infant who should be under close observation by experienced physicians and nurses. Table 97-1 lists the factors that define infants as being high risk. Approximately 10-20% of all births require special or neonatal intensive care. Usually needed for only a few days, such care may last from a few hours to several months. In some institutions, initial care for high-risk infants is provided in a special or transitional care nursery, often within the labor and delivery suite. This facility should be equipped and staffed like a neonatal intensive care area.

Examination of the fresh *placenta*, *cord*, and *membranes* may alert the physician to a newborn infant at high risk and may help confirm a diagnosis in a sick infant. *Fetal blood loss* may be indicated by
Factors That Define an Infant as Being High Risk

The factors that define an infant as being high risk include:

- Meconium staining suggests utero stress and opacity of the fetal surface of the placenta suggests infection. Single umbilical arteries are associated with an increased incidence of congenital renal abnormalities and syndromes.
- For many infants who are born prematurely, are small for gestational age (SGA), have significant perinatal asphyxia, are breech, or are born with life-threatening congenital anomalies, there are no previously identified risk factors. For any given duration of gestation, the lower the birthweight, the higher the neonatal mortality; for any given birthweight, the shorter the gestational duration, the higher the neonatal mortality (Fig. 97-1). The highest risk of neonatal and infant mortality occurs in infants who weigh <1,000 g at birth and whose gestation was <28 wk. The lowest risk of neonatal mortality occurs in infants with a birthweight of 3,000-4,000 g and a gestational age of 39-41 wk. As...
birthweight increases from 400 to 3,000 g and gestational age increases from 23 to 39 wk, a logarithmic decrease in neonatal mortality occurs. In the United States, approximately 50% of all infant deaths occur in infants born after less than 27 wk of gestation or infants weighing less than 1,000 g. Neonatal mortality rates rise sharply for infants weighing more than 4,000 g at birth and for those whose gestational period is 42 wk or longer. Because neonatal mortality largely depends on birthweight and gestational age, Figure 97-1 can be used to help identify high-risk infants quickly. This analysis is based on total live births and therefore describes the mortality risk only at birth. Because most neonatal mortality occurs within the first hours and days after birth, the outlook improves dramatically with increasing postnatal survival. Prediction of death as well as neurodevelopmental impairment improves after birth and continues to improve over the first days and weeks after birth. The importance of gestational age, birth weight, and other perinatal factors for prediction of outcomes decline whereas the importance of respiratory illnesses and other morbidities increase.

97.1 Multiple-Gestation Pregnancies

Waldemar A. Carlo

INCIDENCE

The incidence of spontaneous twinning is highest among blacks and East Indians, followed by northern European whites, and is lowest in the Asian races. Specific rates are 1/56 in Belgium, 1/70 among American blacks, 1/86 in Italy; 1/88 among American whites, 1/130 in Greece, 1/150 in Japan, and 1/300 in China. Differences in the incidence of twins mainly involve fraternal (polyovular) dizygotic twins. Triplets are estimated to occur in 1 in 86 pregnancies and quadruplets in 1 in 86³ pregnancies in the United States. The incidence of monzygotic twins (3-5/1,000) is unaffected by racial or familial factors. The incidence of twins detected by ultrasonography at 12 wk of gestation (3-5%) is much higher than that occurring later in pregnancy; the vanishing twin syndrome results in a singleton fetus. Although the incidence of spontaneous multifetal gestation has been stable over the years, the overall incidence of multifetal gestation is increasing as a result of treatment of infertility with ovarian stimulants (clomiphene, gonadotropins) and in vitro fertilization. Twins account for about 2.5% of births but approximately 15% of extremely low birthweight (ELBW, ≤1,000 g) infants.

ETIOLOGY

The occurrence of monovular twins appears to be independent of genetic influence. Polyovular pregnancies are more frequent beyond the second pregnancy; in older women, and in families with a history of polyovular twins. They may result from simultaneous maturation of multiple ovarian follicles, but follicles containing 2 ova have been described as a genetic trait leading to twin pregnancies. Twin-prone women have higher levels of gonadotropin. Polyovular pregnancies occur in many women treated for infertility.

Conjoined twins (Siamese twins—incidence 1/50,000) result from relatively late monovular separation. The prognosis for conjoined twins depends on the possibility of surgical separation, which, in turn, depends on the extent to which vital organs are shared. The site of connections varies: thoracoamphalopagus (28% of conjoined twins), thoracopagus (18%), omphalopagus (10%), craniopagus (6%), and incomplete duplication (10%). Difficult-to-separate conjoined twins have occasionally survived to adulthood. Most conjoined twins are female.

Superfetation, or fertilization of an ovum by an insemination that takes place after 1 ovum has already been fertilized, and superfetation, or fertilization and subsequent development of an embryo when a fetus is already present in the uterus, have been proposed as uncommon explanations for differences in size and appearance of certain twins at birth. A prenatal diagnosis of pregnancy with twins is suggested by a uterine size that is greater than that expected for gestational age, auscultation of 2 fetal hearts, and elevated maternal serum α-fetoprotein or human chorionic gonadotropin levels, and it is confirmed by ultrasonography.

MONOZYGOTIC VERSUS DIZYGOTIC TWINS

Identifying twins as monzygotic or dizygotic (monovular or polyovular) is useful in determining the relative influence of heredity and environment on human development and disease. Twins not of the same sex are dizygotic. In twins of the same sex, zygosity should be determined and recorded at birth through careful examination of the placenta. Detailed blood typing, gene analysis, or tissue (human leukocyte antigen) typing can also be used to determine zygosity. Monozygotic twins may have physical and cognitive differences because their in utero environment may have been different; differences may exist in the mitochondrial genome, in posttranslational gene product modification, and in the epigenetic modification of nuclear genes in response to environmental factors.

Examination of the Placenta

If the placentas are separate, they are always dichorionic (present in 75%), but the twins are not necessarily dizygotic, because initiation of monovular twinning at the first cell division or during the morula stage may result in 2 amnions, 2 chorions, and even 2 placentas. One-third of monzygotic twins are dichorionic and diamnionic.

An apparently single placenta may be present with either monovular or polyovular twins; yet inspection of a polyovular placenta usually reveals that each twin has a separate chorion that crosses the placenta between the attachments of the cords and two amnions. Separate or fused dichorionic placentas may be disproportionate in size. The fetus attached to the smaller placenta or the smaller portion of the placenta is usually smaller than its twin or is malformed. Monochorionic twins are usually diamnionic, and almost invariably, the placenta is a single mass.

Problems of twin gestation include polyhydramnios, hyperemesis gravidarum, preeclampsia, premature rupture of membranes, vasa previa, velamentous insertion of the umbilical cord, abnormal presentations (breech), and premature labor. Monoamniotic twins have a high fatality rate owing to obstruction of the circulation secondary to intertwining of the umbilical cords. Twins of widely discrepant size are usually monochorionic.

When compared with the first-born twin, the second twin is at increased risk for respiratory distress syndrome and asphyxia. Twins are at risk for IUGR, twin–twin transfusion, and congenital anomalies, which occur predominantly in monzygotic twins. Anomalies are a result of compression deformation of the uterus from crowding (lip dislocation), vascular communication with embolization (ileal atresia, porencephaly, cutis aplasia) or without embolization (acardiac twin), and unknown factors that cause twinning (conjoined twins, anencephaly, meningomyelocele).

Placental vascular anastomoses occur with high frequency only in monochorionic twins. In monochorionic placentas, the fetal vasculature is usually joined, sometimes in a very complex manner. The vascular anastomoses in monochorionic placentas may be artery to artery, vein to vein, or artery to vein. They are usually balanced so that neither twin suffers. Artery-to-artery communications cross over placental veins, and when anastomoses are present, blood can readily be stroked from one fetal vascular bed to the other. Vein-to-vein communications are similarly recognized but are less common. A combination of artery-to-artery and vein-to-vein anastomoses is associated with the condition of acardiac fetus. This rare lethal anomaly (1/35,000) is secondary to the TRAP (twin reversed arterial perfusion) syndrome. In utero neodymium:yttrium-aluminum-garnet (Nd:YAG) laser ablation of the anastomosis or cord occlusion can be used to treat heart failure in the surviving twin. In rare cases, 1 umbilical cord may arise from the other after leaving the placenta. In such cases, the twin attached to the secondary cord usually is malformed or dies in utero.

In the fetal transfusion syndrome, an artery from 1 twin acutely or chronically delivers blood that is drained into the vein of the other. The
The Characteristic Changes in Monochorionic Prematurity to asphyxia. Theoretically, the second twin is more subject to anoxia have an increased likelihood of entangling the cords, which may lead to an increased likelihood of entangling the cords, which may lead to mortality of twins is about 4 times that of singletons. Monoamnionic twins have a significantly higher perinatal mortality, than the first because the placenta may separate after birth of the first twin and before birth of the second. In addition, delivery of the second twin may be difficult because it may be in an abnormal presentation (breech, entangled), uterine tone may be decreased, or the cervix may begin to close after the first twin's birth. Treatment of this problem includes maternal digoxin, aggressive amnioreduction for polyhydramnios, selective twin termination, and Nd: YAG laser or fetoscopic ablation of the anastomosis.

Table 97-2

<table>
<thead>
<tr>
<th>Arterial Side—Donor</th>
<th>Venous Side—Recipient</th>
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<tbody>
<tr>
<td>Prematurity</td>
<td>Prematurity</td>
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<tr>
<td>Oligohydramnios</td>
<td>Polyhydramnios</td>
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<tr>
<td>Small premature</td>
<td>Hydrops</td>
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<td>Large premature</td>
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<tr>
<td>Pale</td>
<td>Well nourished</td>
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<td>Plethoric</td>
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<td>Polycythemic</td>
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<td>Hypoglycemia</td>
<td>Hypervolemic</td>
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<td>Microcardia</td>
<td>Cardiac hypertrophy</td>
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<tr>
<td>Glomeruli small or normal</td>
<td>Myocardial dysfunction</td>
</tr>
<tr>
<td>Arterioles thin walled</td>
<td>Tricuspid valve regurgitation</td>
</tr>
<tr>
<td></td>
<td>Right ventricular outflow obstruction</td>
</tr>
<tr>
<td></td>
<td>Glomeruli large</td>
</tr>
<tr>
<td></td>
<td>Arterioles thick walled</td>
</tr>
</tbody>
</table>

Postnatal Identification

The following physical criteria can be used to determine whether twins are monovular: (1) both must be of the same sex; (2) their features, including ears and teeth, must be obviously alike (but they need not resemble each other more than the lateral halves of one individual); (3) their hair must be identical in color, texture, natural curl, and distribution; (4) their eyes must be of the same color and shade; (5) their skin must be of the same texture and color (nevi may be differently apportioned and distributed); (6) their hands and feet must be of the same conformation and of similar size; and (7) their anthropometric values must show close agreement.

PROGNOSIS

Most twins are born prematurely, and maternal complications of pregnancy are more common than with single pregnancies. The risk for twins is most often associated with twin—twin transfusion, assisted reproductive technology, and early-onset discordant growth. Although monochorionic twins have a significantly higher perinatal mortality, there is no significant difference between the neonatal mortality rates of twin births and single births in comparable weight and gestational age groups (Fig. 97-2). Because most twins are premature, their overall mortality is higher than that of single-birth infants. The perinatal mortality of twins is about 4 times that of singletons. Monoamnionic twins have an increased likelihood of entangling the cords, which may lead to asphyxia. Theoretically, the second twin is more subject to anoxia than the first because the placenta may separate after birth of the first twin and before birth of the second. In addition, delivery of the second twin may be difficult because it may be in an abnormal presentation (breech, entangled), uterine tone may be decreased, or the cervix may begin to close after the first twin's birth. Treatment of this problem includes maternal digoxin, aggressive amnioreduction for polyhydramnios, selective twin termination, and Nd: YAG laser or fetoscopic ablation of the anastomosis.

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TREATMENT

Prenatal diagnosis enables the obstetrician and pediatrician to anticipate the birth of infants who are at high risk because of twinning. Close observation is indicated during labor and in the immediate neonatal period so that prompt treatment of asphyxia or fetal transfusion syndrome can be initiated. The decision to perform an immediate blood transfusion in a severely anemic “donor twin” or to perform a partial exchange transfusion of a “recipient twin” must be based on clinical judgment.

Bibliography is available at Expert Consult.

97.2 Prematurity and Intrauterine Growth Restriction

Waldemar A. Carlo

DEFINITIONS

Traditionally, a delivery date is determined 280 days after the last menstrual period; however, only 4% deliver at 280 days and only 70%...
Bibliography
deliver within 10 days of the estimated delivery date. Human gestation length from ovulation to birth may be 268 days, with a range of 37 days.

Liveborn infants delivered before 37 wk from the 1st day of the last menstrual period are termed premature by the World Health Organization. Low birthweight (LBW; birthweight of 2,500 g or less) is a consequence of prematurity, poor intrauterine growth (IUGR, also referred to as SGA), or both.

The American College of Obstetrics and Gynecology redefines term into subgroups: early term (37 0/7 wk of gestation to 38 6/7 wk), full term (39 0/7–40 6/7 wk), and late term (41 0/7–41 6/7 wk). Early term was previously referred to as late preterm.

Prematurity and IUGR are associated with increased neonatal morbidity and mortality. Ideally, definitions of LBW for individual populations should be based on data that are as genetically and environmentally homogeneous as possible. As previously mentioned, Figure 97-1 presents variations in mortality based on birthweight, gestational age, and gender.

INCIDENCE

There is an increasing percentage of deaths in children <5 yr of age that occur in the neonatal period. More than 5% of deaths in children <5 yr of age occur within the 1st mo of life, with about half of the deaths attributable to prematurity. Approximately 8% of liveborn neonates in the United States weigh <2,500 g; the rate for blacks is almost twice that for whites. Over the past 2 decades, the LBW rate has increased primarily because of an increased number of preterm births registered as live births. Women whose first births are delivered before term are at increased risk for recurrent preterm delivery. Approximately 30% of LBW infants in the United States have IUGR and are born after 37 wk of gestation. At LBW rates >10%, the contribution of IUGR increases and that of prematurity decreases. In developing countries, approximately 70% of LBW infants have IUGR. Infants with IUGR have greater morbidity and mortality than do appropriately grown, gestational age–matched infants (see Fig. 97-1). Although U.S. infant mortality rates have fallen since 1971, the ethnic disparity between black infants and white or Hispanic infants remains unchanged. Black infants have higher neonatal mortality rates and comprise a larger percentage of low birthweight births in the United States.

The incidence of preterm births in the United States continues to rise (Figs. 97-3 and 97-4) and is partly a result of multiple gestation pregnancies and increased reporting as live births of the most immature babies.

VERY LOW BIRTHWEIGHT INFANTS

Very-low birthweight (VLBW) infants weigh <1,500 g and are predominantly premature. In the United States in 2011, the VLBW rates were approximately 1.44% overall, 2.99% among blacks, and 1.14% among whites. The VLBW rate is an accurate predictor of the infant mortality rate. VLBW infants account for more than 50% of neonatal deaths and 50% of handicapped infants; their survival is directly related to birthweight, with approximately 20% of those between 500 and 600 g and >90% of those between 1,250 and 1,500 g surviving. The VLBW rate has remained unchanged for black Americans but has increased among whites, perhaps because of a rise in multiple births among whites. Perinatal care has improved the rate of survival of VLBW infants. When compared with term infants, VLBW neonates have a higher incidence of rehospitalization during the 1st yr of life for sequelae of prematurity, infections, neurologic complications, and psychosocial disorders.

FACTORS RELATED TO PREMATURE BIRTH AND LOW BIRTHWEIGHT

It is difficult to separate completely the factors associated with prematurity from those associated with IUGR (see Chapters 94 and 95). A strong positive correlation exists between both preterm birth and IUGR and low socioeconomic status. Families of low socioeconomic status have higher rates of maternal undernutrition, anemia, and illness; inadequate prenatal care; drug misuse; obstetric complications; and maternal history of reproductive inefficiency (abortions, stillbirths, premature or LBW infants). Other associated factors, such as single-parent families, teenage pregnancies, short interpregnancy interval, and mothers who have borne more than 4 previous children, are also encountered more frequently in such families. Systematic differences in fetal growth have also been described in association with maternal size, birth order, sibling weight, social class, maternal smoking, and other factors. The degree to which the variance in birthweight among various populations is caused by environmental (extrafetal) rather than genetic differences in growth potential is difficult to determine.

The etiology of preterm birth is multifactorial and involves a complex interaction between fetal, placental, uterine, and maternal factors (Table 97-3).

Premature birth of infants whose LBW is appropriate for their preterm gestational age is associated with medical conditions characterized by an inability of the uterus to retain the fetus, interference with the course of the pregnancy, premature rupture of the amniotic membranes or premature separation of the placenta, multifetal gestation, or an undetermined stimulus to effective uterine contractions before term.

Overt or asymptomatic bacterial infection (group B streptococci, *Listeria monocytogenes*, *Ureaplasma urealyticum*, *Mycoplasma hominis*, *Chlamydia*, *Trichomonas vaginalis*, *Gardnerella vaginalis*, *Bacteroides* spp.) of the amniotic fluid and membranes (chorioamnionitis) may initiate preterm labor. Bacterial products may stimulate the production
The 823 Factors Often Associated with Intrauterine Identifiable Causes of Preterm Birth

**Fetal**
- Fetal distress
- Multiple gestation
- Erythroblastosis
- Nonimmune hydrops

**Placental**
- Placental dysfunction
- Placenta previa
- Abruptio placentae

**Uterine**
- Bicornuate uterus
- Incompetent cervix (premature dilation)

**Maternal**
- Preeclampsia
- Chronic medical illness (cyanotic heart disease, renal disease)
- Infecion (Listeria monocytogenes, group B streptococcus, urinary tract infection, bacterial vaginosis, chorioamnionitis)
- Drug abuse (cocaine)

**Other**
- Premature rupture of membranes
- Polyhydramnios
- Iatrogenic
- Trauma

IUGR is associated with medical conditions that interfere with the circulation and efficiency of the placenta, with the development or growth of the fetus, or with the general health and nutrition of the mother (Table 97-4). Many factors are common to both prematurely born and LBW infants with IUGR. IUGR is associated with decreased insulin production or insulin (or insulin-like growth factor) action at the receptor level. Infants with insulin-like growth factor-1 receptor defects, pancreatic hypoplasia, or transient neonatal diabetes have IUGR. Genetic mutations affecting the glucose-sensing mechanisms of the pancreatic islet cells that result in decreased insulin release (loss of function of the glucose-sensing glucokinase gene) give rise to IUGR.

IUGR may be a normal fetal response to nutritional or oxygen deprivation. Therefore, the issue is not the IUGR but rather the ongoing risk of fetal malnutrition or hypoxia. Similarly, some preterm births signify a need for early delivery from a potentially disadvantageous intrauterine environment. IUGR is often classified as reduced growth that is symmetric (head circumference, length, and weight equally affected) or asymmetric (with relative sparing of head growth) (see Fig. 96-1 in Chapter 96). Symmetric IUGR often has an earlier onset and is associated with diseases that seriously affect fetal cell number, such as conditions with chromosomal, genetic, malformation, teratogenic, infectious, or severe maternal hypertensive etiologies. It is important to assess gestational age carefully in infants suspected to have symmetric IUGR because incorrect overestimation of gestational age may lead to the diagnosis of symmetric IUGR. Asymmetric IUGR is often of late onset, demonstrates preservation of Doppler waveform velocity to the carotid vessels, and is associated with poor maternal nutrition or with late onset or exacerbation of maternal vascular...
disease (preeclampsia, chronic hypertension). Table 97-5 lists the problems of infants with IUGR.

**ASSESSMENT OF GESTATIONAL AGE AT BIRTH**

When compared with a premature infant of appropriate weight, an infant with IUGR has a reduced birthweight and may appear to have a disproportionately larger head relative to body size; infants in both groups lack subcutaneous fat. Neurologic maturity (nerve conduction velocity) in the absence of asphyxia correlates with gestational age despite reduced fetal weight. Physical signs may be useful in estimating gestational age at birth. Commonly used, the Ballard scoring system is accurate to ±2 wk (Figs. 97-5 to 97-7). An infant should be presumed to be at high risk for mortality or morbidity if a discrepancy exists between the estimation of gestational age by physical examination, the mother's estimated date of her last menstrual period, and fetal ultrasonographic evaluation.

**SPECTRUM OF DISEASE IN LOW-BIRTHWEIGHT INFANTS**

Immaturity increases the severity but reduces the distinctiveness of the clinical manifestations of most neonatal diseases. Immature organ function, complications of therapy, and the specific disorders that caused the premature onset of labor contribute to the neonatal

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### Table 97-5

<table>
<thead>
<tr>
<th>PROBLEM</th>
<th>PATHOGENESIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrauterine fetal demise</td>
<td>Hypoxia, acidosis, infection, lethal anomaly</td>
</tr>
<tr>
<td>Perinatal asphyxia</td>
<td>↓ Uteroplacental perfusion during labor ↓ chronic fetal hypoxia–acidosis; meconium aspiration syndrome</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>↓ Tissue glycogen stores, ↓ gluconeogenesis, hyperinsulinism, ↑ glucose needs of hypoxia, hypothermia, large brain</td>
</tr>
<tr>
<td>Polycythemia–hyperviscosity</td>
<td>Fetal hypoxia with ↑ erythropoietin production</td>
</tr>
<tr>
<td>Reduced oxygen consumption/hypothermia</td>
<td>Hypoxia, hypoglycemia, starvation effect, poor subcutaneous fat stores</td>
</tr>
<tr>
<td>Dysmorphology</td>
<td>Syndrome anomalies, chromosomal-genetic disorders, oligohydramnios-induced deformation, TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex) infection</td>
</tr>
</tbody>
</table>

*Other problems include pulmonary hemorrhage and those common to the gestational age-related risks of prematurity if born at less than 37 wk. ↓, Decreased; ↑, increased.

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### Figure 97-6

Neuromuscular criteria for maturity. The expanded New Ballard score includes extremely premature infants and has been refined to improve accuracy in more mature infants. *(From Ballard JL, Khoury JC, Wedig K, et al: New Ballard score, expanded to include extremely premature infants, J Pediatr 119:417–423, 1991.)*

### Figure 97-5

Physical criteria for maturity. The expanded New Ballard score includes extremely premature infants and has been refined to include extremely premature infants, J Pediatr 119:417–423, 1991.)*

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</tr>
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### Figure 97-5

Physical criteria for maturity. The expanded New Ballard score includes extremely premature infants and has been refined to improve accuracy in more mature infants, J Pediatr 119:417–423, 1991.)
The neonatal problems associated with the infant's core temperature is within the normal range. The neutral (measured experimentally as oxygen consumption) is minimal and temperatures, relative humidity, and airflow, at which heat production is a set of thermal conditions, including air and radiating surface temperatures. Careful monitoring to avoid the risk of serious hypothermia when smaller, younger infants do. Incubators or radiant warmers can be used to maintain body temperature. Body heat is conserved through provision of a warm environment and humidity. The optimal environmental temperature required. An additional acrylic resin (Plexiglas) heat shield or head cap and body clothing may be required to keep an infant; larger, older infants require lower environmental temperatures than smaller, younger infants do. Incubators or radiant warmers can be used to maintain body temperature. Body heat is conserved through provision of a warm environment and humidity. The optimal environmental temperature is a function of the size and postnatal age of an infant; larger, older infants require lower environmental temperatures than smaller, younger infants do. Incubators or radiant warmers can be used to maintain body temperature. Body heat is conserved through provision of a warm environment and humidity. The optimal environmental temperature required. An additional acrylic resin (Plexiglas) heat shield or head cap and body clothing may be required to keep an extremely LBW (ELBW) preterm infant warm. Infant warmth can be maintained by heating the air to a desired temperature or by servocontrolling the infant's body temperature at a desired set point. Continuous monitoring of the infant's temperature is required so that the environmental temperature can be adjusted to maintain optimal body temperature.

**NURSERY CARE**

At birth, the measures needed to clear the airway, initiate breathing, care for the umbilical cord and eyes, and administer vitamin K are the same for immature infants as for those of normal weight and maturity (see Chapter 94). Special care is required to maintain a patent airway. Additional considerations are the need for (1) thermal control and monitoring of the heart rate and respiration, (2) oxygen therapy, and (3) special attention to the details of fluid requirements and nutrition. Safeguards against infection can never be relaxed. Routine procedures that disturb these infants may result in hypoxia. The need for regular and active participation by the parents in the infant's care in the nursery, the need to instruct the mother in at-home care of her infant, and the question of prognosis for later growth and development require special consideration.

**Thermal Control**

The survival rate of LBW and sick infants is higher when they are cared for at or near their neutral thermal environment. This environment is a set of thermal conditions, including air and radiating surface temperatures, relative humidity, and airflow, at which heat production (measured experimentally as oxygen consumption) is minimal and the infant's core temperature is within the normal range. The neutral thermal environment is a function of the size and postnatal age of an infant; larger, older infants require lower environmental temperatures than smaller, younger infants do. Incubators or radiant warmers can be used to maintain body temperature. Body heat is conserved through provision of a warm environment and humidity. The optimal environmental temperature for minimal heat loss and oxygen consumption for an unclothed infant is one that maintains the infant's core temperature at 36.5-37.0°C (97.7-98.6°F). It depends on an infant's size and maturity; the smaller and more immature the infant, the higher the environmental temperature required. An additional acrylic resin (Plexiglas) heat shield or head cap and body clothing may be required to keep an extremely LBW (ELBW) preterm infant warm. Infant warmth can be maintained by heating the air to a desired temperature or by servocontrolling the infant's body temperature at a desired set point. Continuous monitoring of the infant's temperature is required so that the environmental temperature can be adjusted to maintain optimal body temperature. Kangaroo mother care with direct skin-to-skin contact and a hat and blanket covering the infant is a safe alternative, with careful monitoring to avoid the risk of serious hypothermia when

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**Table 97-6 Neonatal Problems Associated with Premature Infants**

<table>
<thead>
<tr>
<th>Category</th>
<th>Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RESPIRATORY</strong></td>
<td>Respiratory distress syndrome (hyaline membrane disease)*</td>
</tr>
<tr>
<td></td>
<td>Bronchopulmonary dysplasia</td>
</tr>
<tr>
<td></td>
<td>Pneumothorax, pneumomediastinum; interstitial emphysema</td>
</tr>
<tr>
<td></td>
<td>Congenital pneumonia</td>
</tr>
<tr>
<td></td>
<td>Apnea*</td>
</tr>
<tr>
<td><strong>CARDIOVASCULAR</strong></td>
<td>Patent ductus arteriosus*</td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td>Bradycardia (with apnea)*</td>
</tr>
<tr>
<td><strong>HEMATOLOGIC</strong></td>
<td>Anemia (early or late onset)</td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL</strong></td>
<td>Poor gastrointestinal function—poor motility*</td>
</tr>
<tr>
<td></td>
<td>Necrotizing enterocolitis</td>
</tr>
<tr>
<td></td>
<td>Hyperbilirubinemia—direct and indirect*</td>
</tr>
<tr>
<td></td>
<td>Spontaneous gastrointestinal isolated perforation</td>
</tr>
<tr>
<td><strong>METABOLIC-ENDOCRINE</strong></td>
<td>Hypocalcemia*</td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia*</td>
</tr>
<tr>
<td></td>
<td>Hyperglycemia*</td>
</tr>
<tr>
<td></td>
<td>Late metabolic acidosis</td>
</tr>
<tr>
<td></td>
<td>Hypothermia*</td>
</tr>
<tr>
<td></td>
<td>Euthyroid but low thyroxine status</td>
</tr>
<tr>
<td></td>
<td>Osteopenia</td>
</tr>
<tr>
<td><strong>CENTRAL NERVOUS SYSTEM</strong></td>
<td>Intraventricular hemorrhage*</td>
</tr>
<tr>
<td></td>
<td>Periventricular leukomalacia</td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
</tr>
<tr>
<td></td>
<td>Retinopathy of prematurity</td>
</tr>
<tr>
<td></td>
<td>Deafness</td>
</tr>
<tr>
<td></td>
<td>Hypotonia*</td>
</tr>
<tr>
<td><strong>RENAL</strong></td>
<td>Hyponatremia*</td>
</tr>
<tr>
<td></td>
<td>Hypernatremia*</td>
</tr>
<tr>
<td></td>
<td>Hyperkalemia*</td>
</tr>
<tr>
<td></td>
<td>Renal tubular acidosis</td>
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<td></td>
<td>Renal glycosuria</td>
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<tr>
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<td>Edema</td>
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<td><strong>GASTROINTESTINAL</strong></td>
<td>Spontaneous gastrointestinal isolated perforation</td>
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<tr>
<td><strong>HEMATOLOGIC</strong></td>
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<tr>
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<td>Hyponatremia*</td>
</tr>
<tr>
<td></td>
<td>Hypernatremia*</td>
</tr>
<tr>
<td></td>
<td>Hyperkalemia*</td>
</tr>
<tr>
<td><strong>OTHER</strong></td>
<td>Congenital pneumonia</td>
</tr>
<tr>
<td></td>
<td>Perinatal, nosocomial: bacterial, viral, fungal, protozoal</td>
</tr>
</tbody>
</table>

*Common.

**Table 97-6 Maturity Rating**

<table>
<thead>
<tr>
<th>Score</th>
<th>Weeks</th>
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<tr>
<td>–10</td>
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</tr>
<tr>
<td>–5</td>
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</tr>
<tr>
<td>0</td>
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</tr>
<tr>
<td>5</td>
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<td>45</td>
<td>42</td>
</tr>
<tr>
<td>50</td>
<td>44</td>
</tr>
</tbody>
</table>

**Figure 97-7 Maturity Rating** The physical and neurologic scores are added to calculate gestational age. (From Ballard JL, Khoury JC, Wedig K, et al: New Ballard score, expanded to include extremely immature infants, J Pediatr 119:417-423, 1991.)
incubators are unavailable or when the infant is stable and the parent desire close contact with their infant.

Maintaining a relative humidity of 40-60% aids in stabilizing body temperature by reducing heat loss at lower environmental temperatures; by preventing dryness and irritation of the lining of respiratory passages, especially during the administration of oxygen and after or during endotracheal intubation (usually 100% humidity); and by thinning viscid secretions and reducing insensible water loss from the lungs. An infant should be weaned and then removed from the incubator or radiant warmer only when the gradual change to the atmosphere of the nursery does not result in a significant change in the infant's temperature, color, activity, or vital signs.

Administering oxygen to reduce the risk of injury from hypoxia and circulatory insufficiency must be balanced against the risk of hyperoxia to the eyes (retinopathy of prematurity) and oxygen injury to the lungs. Oxygen should be administered via a head hood, nasal cannula, continuous positive airway pressure apparatus, or endotracheal tube to maintain stable and safe inspired oxygen concentrations. Although cyanosis must be treated immediately, oxygen is a drug, and its use must be carefully regulated to maximize benefit and minimize potential harm. The concentration of inspired oxygen must be adjusted in accordance with the oxygen tension of arterial blood (PaO₂) or a noninvasive method such as continuous pulse oximetry or transcutaneous oxygen measurements. Capillary blood gas determinations are inadequate for estimating arterial oxygen levels.

Fluid Requirements
Fluid needs vary according to gestational age, environmental conditions, and disease states. Assuming minimal water loss in the stool of infants not receiving oral fluids, their water needs are equal to their insensible water loss, excretion of renal solutes, growth, and any unusual ongoing losses. Insensible water loss is indirectly related to gestational age; very immature preterm infants (<1,000 g) may lose as much as 2-3 mL/kg/hr, partly because of immature skin, lack of subcutaneous tissue, and a large exposed surface area. Insensible water loss is increased under radiant warmers, during phototherapy, and in febrile infants. High humidity can be used to reduce insensible water losses. The loss is diminished when an infant is clothed, is covered by an acrylic resin inner heat shield, breathes humidified air, or is of advanced postnatal age. A larger premature infant (2,000-2,500 g) may lose as much as 2-3 mL/kg/hr, partly because of immature skin, lack of subcutaneous tissue, and a large exposed surface area. Insensible water loss is increased under radiant warmers, during phototherapy, and in febrile infants. High humidity can be used to reduce insensible water losses. The loss is diminished when an infant is clothed, is covered by an acrylic resin inner heat shield, breathes humidified air, or is of advanced postnatal age. A larger premature infant (2,000-2,500 g) nursed in an incubator may have an insensible water loss of approximately 0.6-0.7 mL/kg/hr.

Adequate fluid intake is essential for excretion of the urinary solute load (urea, electrolytes, phosphate). The amount varies with dietary intake and the anabolic or catabolic state of nutrition. Formulas with a high solute load, high protein intake, and catabolism increase the end products that require urinary excretion and thus increase the requirement for water. Renal solute loads may vary between 7.5 and 30 mOsm/kg. Newborn infants, especially VLBW ones, are also less able to concentrate urine, so they need higher fluid intake to excrete solutes.

Fluid intake in term infants is usually begun at 60-70 mL/kg on day 1 and increased to 100-120 mL/kg by days 2-3. Smaller, more premature infants may need to start with 70-80 mL/kg on day 1 and advance gradually to 150 mL/kg/day. Fluid volumes should be titrated individually, although it is unusual to exceed 150 mL/kg/24 hr. Infants weighing <750 g in the 1st wk of life have immature skin and a large surface area, characteristics that lead to a high rate of transepidermal fluid loss, at times requiring higher rates of intravenous fluids. Daily weights, urine output, and serum urea nitrogen and sodium levels should be monitored carefully to determine water balance and fluid needs. Clinical observation and physical examination are poor indicators of the state of hydration of premature infants. Conditions that increase fluid loss, such as glycosuria, the polyuric phase of acute tubular necrosis, and diarrhea, may place additional strain on kidneys that have not yet acquired their maximal capacity to conserve water and electrolytes, the result of which may be severe dehydration. Alternatively, fluid overload may lead to edema, heart failure, patent ductus arteriosus, and bronchopulmonary dysplasia.

Parenteral Nutrition
Before complete enteral feeding has been established or when enteral feeding is impossible for prolonged periods, total intravenous alimentation may provide sufficient fluid, calories, amino acids, electrolytes, and vitamins to sustain the growth of ill infants. This technique has been lifesaving for VLBW and preterm infants and infants who had intractable diarrheal syndromes or extensive bowel resection. Infusions may be administered through a percutaneously or, less often, surgically placed indwelling central venous catheter or through a peripheral vein. The umbilical vein may also be used for up to 2 wk. The goal of parenteral alimentation is to deliver sufficient calories from glucose, protein, and lipids to promote optimal growth. The infusion should contain 2.5-3.5 g/dL of synthetic amino acids and usually 10-15 g/dL of glucose, in addition to appropriate quantities of electrolytes, trace minerals, and vitamins. If a peripheral vein is used, it is advisable to keep the glucose concentration below 12.5 g/dL. If a central vein is used, glucose concentrations as high as 25 g/dL may be used (rarely). Intravenous fat emulsions such as Intralipid 20% (2.2 kcal/mL) may be administered to provide calories without an appreciable osmotic load, thereby decreasing the need for infusion of the higher concentrations of glucose by central or peripheral vein while preventing the development of essential fatty acid deficiency. A 20% fat emulsion may be initiated at 0.5 g/kg/24 hr and advanced to 3 g/kg/24 hr, if triglyceride levels remain normal; 0.5 g/kg/24 hr is sufficient to prevent essential fatty acid deficiency. Electrolytes, trace minerals, and vitamin additives are included in amounts approximating established intravenous maintenance requirements. The content of each day's infusate should be determined after careful assessment of the infant's clinical and biochemical status. Slow and continuous infusion is advisable. A well-trained pharmacist should mix all solutions under a laminar flow hood.

After a caloric intake of >100 kcal/kg/24 hr is established by total parenteral intravenous nutrition, the infants can be expected to gain about 15 g/kg/24 hr, with a positive nitrogen balance of 150-200 mg/kg/24 hr, in the absence of episodes of sepsis, surgical procedures, and other severe stress. This goal can usually be achieved (and the catabolic tendency during the 1st wk of life reversed, with subsequent weight gain) by peripheral vein infusion of 2.5-3.5 g/kg/24 hr of an amino acid mixture, 10 g/dL of glucose, and 2-3 g/kg/24 hr of a 20% fat emulsion.

Complications of intravenous alimentation are related to both the catheter and the metabolism of the infusate. Sepsis, the most important problem of central vein infusions, can be minimized only by meticulous catheter care and aseptic preparation of the infusate; a vancomycin–heparin solution also reduces the risk of line sepsis. Coagulase-negative Staphylococcus is the most common infecting organism. Treatment includes appropriate antibiotics. If an infection persists (repeatedly positive blood culture results while the infant is receiving appropriate antibiotics), the line must be removed. Thrombosis, extravasation of fluid, and accidental dislodgment of catheters have also occurred. Although sepsis is less often attributable to peripheral vein infusion, phlebitis, cutaneous sloughing, and superficial infection may occur. Metabolic complications of parenteral nutrition include hyperglycemia from the high glucose concentration of the infusate, which may lead to osmotic diuresis and dehydration; azotemia; a possible increased risk of nephrocalcinosis; hypoglycemia from sudden accidental cessation of the infusate; hyperlipidemia and possibly hypoxemia from intravenous lipid infusions; and hyperammonemia, which may result from high levels of certain amino acids. Metabolic bone disease and/or cholestatic jaundice and liver disease may develop in infants who require long-term parenteral nutrition and receive no enteral nutrition. Biochemical and physiologic monitoring of infants receiving intravenous alimentation is indicated because of the frequency and seriousness of complications.

Feeding
The method of feeding each LBW or preterm infant should be individualized. It is important to avoid fatigue and aspiration of food.
through regurgitation or the feeding process. No feeding method avoids these problems unless the person feeding the infant has been well trained in the method. Oral feeding ( nipple) should not be initiated or should be discontinued in infants with respiratory distress, hypoxia, circulatory insufficiency, excessive secretions, gagging, sepsis, central nervous system depression, severe immaturity, or signs of serious illness. These high-risk infants require parenteral nutrition or gavage feeding to supply calories, fluid, and electrolytes. The process of oral alimenation requires, in addition to a strong sucking effort, coordination of swallowing, epiglottal and uvalar closure of the larynx and nasal passages, and normal esophageal motility; a synchronized process that is usually absent before 34 wk of gestation.

Preterm infants at 34 wk of gestation or more can often be fed by bottle or at the breast. Because the effort of sucking is usually the limiting factor, direct breastfeeding is less likely to succeed in very preterm infants until they mature. Bottle-feeding of expressed breast milk may be a temporary alternative. In bottle-feeding, the infant’s effort may be reduced by use of special small, soft nipples with large holes. Smaller or less vigorous infants should be fed by gavage: A soft plastic tube with No. 5 French external and approximately 0.05 cm internal diameters and with a rounded atraumatic tip and two holes on alternate sides is preferable. The tube is passed through the nose until approximately 2.5 cm (1 inch) of the lower end is in the stomach. The free end of the tube has an adapter into which the tip of a syringe is fitted, and a measured amount of fluid is given by pump or by gravity. Such a tube may be left in place for 3-7 days before being replaced by a similar tube through the other nostril. Infants occasionally have enough local irritation from an indwelling tube that they may gag or troublesome secretions may gather around it in the nasopharynx. In such cases, a catheter may be passed through the mouth by a skilled person and removed at the end of each feeding.

The infant may be fed with intermittent bolus feedings or continuous feeding. In the occasional infant with feeding intolerance, nasojejunal feeding may be successful. Intestinal perforation is a risk with nasojejunal feeding. A change to breast- or bottle-feeding may be instituted gradually as soon as an infant displays general vigor adequate for oral feeding without fatigue.

Gastrostomy feeding is not usually indicated in premature or LBW infants except as an adjunct to surgical management of specific gastrointestinal conditions or in patients with permanent neurologic injuries who are unable to suck and swallow normally.

**Initiation of Feeding**

The optimal time to introduce enteral feeding to a sick premature or LBW infant is controversial. Trophic feeding is the practice of feeding very small amounts of enteral nourishment to VLBW preterm infants to stimulate development of the immature gastrointestinal tract. The benefits of trophic feeding include enhanced gut motility, improved growth, decreased need for parenteral nutrition, fewer episodes of sepsis, and shortened hospital stay. Once the infant is stable, small-volume feedings are given in addition to intravenous fluids/nutrition. Trophic feeding appears to stop feedings, at least temporarily, and to increase subsequent feedings slowly only as tolerated or to change to intravenous alimentation and evaluate the infant for more serious problems (see Chapter 102.2). Weight gain may not be achieved for 10-12 days. Alternatively, in infants whose feeding schedule is advanced successfully in calories or volume, weight gain may appear within a few days.

When tube feeding is used, the contents of the stomach should be aspirated before each feeding. If only air or small amounts of mucus are obtained, the feeding is given as planned. If all or a substantial part of the previous feeding is aspirated, it is advisable to withhold feedings or to reduce the amount of the feeding and proceed more gradually with subsequent increases, depending on the physical findings and other evidence of feeding intolerance.

The digestive enzyme systems of infants older than 28 wk of gestation are mature enough to permit adequate digestion and absorption of protein and carbohydrate. Fat is less well absorbed, primarily because of inadequate amounts of bile salt; unsaturated fats and the fat of human milk are absorbed better than the fat of cow’s milk. The weight gain of infants weighing <2,000 g at birth should be adequate when either human milk or “humanized” milk premature formula (40% casein and 60% whey) with a protein intake of 2.25-2.75 g/kg/24 hr is fed. These 2 alternatives should provide all amino acids essential for premature infants, including tyrosine, cystine, and histidine. Higher protein intake may be well tolerated and is generally safe, especially in older, rapidly growing infants. Protein intake >4.5 g/kg/24 hr may be hazardous. Although they may promote linear growth, high-protein formulas may cause abnormal plasma
aminogram results; elevations in blood urea nitrogen, ammonia, and sodium concentrations; metabolic acidosis (cow's milk formulas); and untoward effects on neurologic development. Furthermore, the high protein and mineral contents of balanced cow's milk formulas with a high caloric content constitute a large solute load for the kidneys, a fact important in maintaining water balance, especially in infants with diarrhea or fever.

**Breast milk** from their mothers is the preferred milk for all infants, including VLBW infants. In addition to nutritional advantages, the benefits of breast milk include protection against a wide range of infections (through both specific and nonspecific anti-infective factors in breast milk and beneficial effects on intestinal flora), a decreased risk of necrotizing enterocolitis in preterm infants, a lower risk of sudden infant death syndrome, and possible long-term effects, including a lower risk of childhood/adolescent obesity and improved neurodevelopmental outcome. Once a premature infant takes 120 mL/kg/24 hr, **breast milk fortifiers** are added to supplement breast milk with protein, calcium, and phosphorus. If breast milk is unavailable, special preterm formulas should be used.

Properly fed premature infants may have from 1 to 8 daily stools of semisolid consistency; a sudden increase in their number, the appearance of occult or gross blood, or change to a watery consistency is more reason for concern than any arbitrarily stated stooling frequency.

**Vitamins**

Although formula in amounts necessary for adequate growth probably contains adequate quantities of all vitamins, the volume of milk sufficient to satisfy these requirements may not be ingested for several weeks. Therefore, LBW and preterm infants should be given supplemental vitamins. Because requirements for these infants have not been precisely established, the recommended daily allowances for term infants should be given (see Chapter 44). Furthermore, infants may have a special need for certain vitamins. Intermediary metabolism of phenylalanine and tyrosine depends, in part, on vitamin C. Decreased fat absorption with increased fecal fat loss may be associated with decreased absorption of vitamin D, other fat-soluble vitamins, and calcium in premature infants. VLBW infants are particularly prone to the development of osteopenia, but their total intake of vitamin D should not exceed 1,500 IU/24 hr. Folic acid is essential for the formation of DNA and production of new cells; serum and erythrocyte levels decrease in preterm infants during the first few wk of life and remain low for 2-3 mo. Therefore, folic acid supplementation is recommended, although it does not result in improved growth or an increased hemoglobin concentration. Deficiency of vitamin E is uncommon, but is associated with increased hemolysis and, if severe, with anemia and edema in premature infants. Vitamin E functions as an antioxidant to prevent the peroxidation of excessive polyunsaturated fatty acids in red blood cell membranes; its need may increase because of the higher membrane content of these fatty acids when formulas with high polyunsaturated fatty acids are used. Vitamin A supplementation reduces bronchopulmonary dysplasia in ELBW infants. Vitamin K deficiency is discussed in Chapter 97.4.

In LBW and premature infants, **physiologic anemia** from postnatal suppression of erythropoiesis is exacerbated by smaller fetal iron stores and greater expansion of blood volume from the more rapid growth than that of term infants; therefore, the anemia develops earlier and reaches a lower ultimate level. Fetal or neonatal blood loss accentuates this problem. Iron stores, even in a VLBW neonate, are usually adequate until an infant's birthweight has doubled; iron supplementation (2 mg/kg/24 hr) should then be started. If erythropoietin is used, iron supplementation is also required.

**Prevention of Infection**

Premature infants have an increased susceptibility to infection, and thus meticulous attention to infection control is required. Prevention strategies include strict compliance with handwashing and universal precautions, minimizing the risk of catheter contamination and duration, meticulous skin care, encouraging early appropriate advancement of enteral feeding, education and feedback to staff, and surveillance of nosocomial infection rates in the nursery. Although no one with an active infection should be permitted in the nursery, the risks of infection must be balanced against the disadvantages of limiting the infant's contact with the family. Early and frequent participation by parents in the nursery care of their infant does not increase the risk of infection when preventive precautions are maintained.

Preventing transmission of infection from infant to infant is difficult because often neither term nor premature newborn infants have clear clinical evidence of an infection early in its course. When epidemics occur within a nursery, cohort nursing and isolation rooms should be used. Universal precautions require gloves to be worn with all patient contact. Because premature infants have immature immune function, some will develop nosocomial infection even when all precautions are followed.

Routine immunizations should be given on the regular schedule at standard doses (see Chapter 172).

**IMMATURITY OF DRUG METABOLISM**

Renal clearance of almost all substances excreted in the urine is diminished in newborn infants, but more so in premature ones. The glomerular filtration rate rises with increasing gestational age; therefore drug dosing recommendations vary with age. Intervals between doses may therefore need to be extended with administration of drugs excreted chiefly by the kidneys. Longer intervals are required for many drugs administered to preterm infants. Drugs that are detoxified in the liver or require chemical conjugation before renal excretion should also be given with caution and in doses smaller than usual.

When possible, blood levels should be determined for potentially toxic drugs, especially if renal or hepatic dysfunction is present. Decisions about the choice and dose of antibacterial agents and the route of administration should be made on an individual basis rather than routinely because of the dangers of (a) development of infections with organisms resistant to antibacterial agents, (b) inhibition of intestinal bacteria that manufacture significant amounts of essential vitamins (vitamin K and thiamine), and (c) harmful interference in important metabolic processes.

Many drugs apparently safe for adults on the basis of toxicity studies may be harmful to newborn infants, especially premature ones. Oxygen and a number of drugs have proved toxic to premature infants in amounts not harmful to term infants (Table 97-7). Thus, administering any drug, particularly in high doses, that has not undergone pharmacologic testing in premature infants should be undertaken carefully after risks have been weighed against benefits.

**PROGNOSIS**

Infants born weighing 1,501-2,500 g have a 95% or greater chance of survival, but those weighing still less have significantly higher mortality (see Fig. 97-1). Intensive care has extended the period during which a VLBW infant is at increased risk of dying of complications of prematurity, such as bronchopulmonary dysplasia, necrotizing enterocolitis, and nosocomial infection (Table 97-8). The postdischarge mortality rate of LBW infants is higher than that of term infants during the 1st 2 yr of life. Because many of the deaths are attributable to infection (e.g., respiratory syncytial virus), they are at least theoretically preventable. In addition, premature infants have an increased incidence of failure to thrive, sudden infant death syndrome, child abuse, and inadequate maternal-infant bonding. The biologic risk associated with poor cardiorespiratory regulation as a result of immaturity or complications of underlying perinatal disease and the social risk associated with poverty also contribute to the high mortality and morbidity of these infants. Congenital anomalies are present in approximately 3-7% of LBW infants.

In the absence of congenital abnormalities, central nervous system injury, VLBW, or marked IUGR, the physical growth of LBW infants tends to approximate that of term infants by the 2nd yr; the approximation occurs earlier in premature infants with larger birth size. VLBW infants may not catch up, especially if they have severe chronic sequelae, insufficient nutritional intake, or an inadequate caretaking
environment (see Table 97-8). Infrequently, infants with IUGR (SGA) grow poorly and do not demonstrate catch-up growth. These infants may benefit from recombinant human growth hormone therapy beginning at age 4 yr.

Premature birth in itself may adversely affect later development. The greater the immaturity and the lower the birthweight, the greater the likelihood of intellectual and neurologic deficit; as many as 50% of 500-750 g infants have significant neurodevelopmental impairment (mental retardation, cerebral palsy, blindness, deafness). Small head circumference at birth may be related to a poor neurobehavioral prognosis. Many surviving LBW infants have hypotonia before 8 mo corrected age, which improves by the time they are 8 mo to 1 yr old. This transient hypotonia is not a poor prognostic sign. Thirty percent to 50% of VLBW children have poor school performance at 7 yr of age (repeating of grades, special classes, learning disorders, poor speech and language), despite a normal IQ. Factors posing a risk for poor academic performance include birthweight below 750 g, severe IVH, periventricular leukomalacia, bronchopulmonary dysplasia, cerebral atrophy, posthemorrhagic hydrocephalus, IUGR, low socioeconomic status, and, possibly, low thyroidine levels. Antenatal exposure to magnesium sulfate may have neuroprotective effects and may reduce the incidence of cerebral palsy in high-risk neonates. Adolescents who were VLBW report satisfactory health; 94% are integrated in regular classes despite neurosensory disabilities (hearing, vision, cerebral palsy, cognition) in 24%. Both premature and IUGR infants are at risk for significant metabolic conditions (obesity, type II diabetes) and cardiovascular disorders (ischemic heart disease, hypertension) as adults. This fetal origins hypothesis of adult morbidities may involve insulin resistance, which may be evident in early childhood.

### Table 97-7: Potential Adverse Reactions to Drugs Administered to Premature Infants

<table>
<thead>
<tr>
<th>DRUG</th>
<th>REACTION(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen</td>
<td>Retinopathy of prematurity, bronchopulmonary dysplasia</td>
</tr>
<tr>
<td>Sulfisoxazole</td>
<td>Kernicterus</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Gray baby syndrome—shock, bone marrow suppression</td>
</tr>
<tr>
<td>Vitamin K analogs</td>
<td>Jaundice</td>
</tr>
<tr>
<td>Novobiocin</td>
<td>Jaundice</td>
</tr>
<tr>
<td>Hexachlorophene</td>
<td>Encephalopathy</td>
</tr>
<tr>
<td>Benzyl alcohol</td>
<td>Acidosis, collapse, intraventricular bleeding</td>
</tr>
<tr>
<td>Intravenous vitamin E</td>
<td>Ascites, shock</td>
</tr>
<tr>
<td>Phenolic detergents</td>
<td>Jaundice</td>
</tr>
<tr>
<td>NaHCO₃</td>
<td>Intraventricular hemorrhage</td>
</tr>
<tr>
<td>Amphotericin</td>
<td>Anuric renal failure, hypokalemia, hypomagnesemia</td>
</tr>
<tr>
<td>Reserpine</td>
<td>Nasal stuffiness</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Oliguria, hyponatremia, intestinal perforation</td>
</tr>
<tr>
<td>Cisapride</td>
<td>Prolonged QTc interval</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Enamel hypoplasia</td>
</tr>
<tr>
<td>Tolazoline</td>
<td>Hypotension, gastrointestinal bleeding</td>
</tr>
<tr>
<td>Calcium salts</td>
<td>Subcutaneous necrosis</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Deafness, renal toxicity</td>
</tr>
<tr>
<td>Enteric gentamicin</td>
<td>Resistant bacteria</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>Seizures, diarrhea, apnea, hyperostosis, pyloric stenosis</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Altered state, drowsiness</td>
</tr>
<tr>
<td>Morphine</td>
<td>Hypotension, urine retention, withdrawal</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>Edema, hypovolemia, hypotension, tachycardia, vecuronium contractions, prolonged hypotonia</td>
</tr>
<tr>
<td>Iodine antiseptics</td>
<td>Hypothyroidism, goiter</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Seizures, chest wall rigidity, withdrawal</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Gastrointestinal bleeding, hypertension, infection, hyperglycemia, cardiomyopathy, reduced growth</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Deafness, hyponatremia, hypokalemia, hyphochloremia, nephrocalcinosis, biliary stones</td>
</tr>
<tr>
<td>Heparin (not low-dose prophylactic use)</td>
<td>Bleeding, intraventricular hemorrhage, thrombocytopenia</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Pyloric stenosis</td>
</tr>
</tbody>
</table>

### Table 97-8: Sequelae of Low Birthweight

<table>
<thead>
<tr>
<th>IMMEDIATE</th>
<th>LATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxia, ischemia</td>
<td>Mental retardation, spastic diplegia, microcephaly, seizures, poor school performance</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>Mental retardation, spasticity, seizures, hydrocephalus</td>
</tr>
<tr>
<td>Sensorineural injury</td>
<td>Hearing, visual impairment, retinopathy of prematurity, strabismus, myopia</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>Bronchopulmonary dysplasia, cor pulmonale, bronchospasms, malnutrition, subglotic stenosis</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>Short-bowel syndrome, malabsorption, malnutrition, infectious diarrhea</td>
</tr>
<tr>
<td>Cholestatic liver disease</td>
<td>Cirrhosis, hepatic failure, malnutrition</td>
</tr>
<tr>
<td>Nutrient deficiency</td>
<td>Osteopenia, fractures, anemia, growth failure</td>
</tr>
<tr>
<td>Social stress</td>
<td>Child abuse or neglect, failure to thrive, divorce</td>
</tr>
<tr>
<td>Other</td>
<td>Sudden infant death syndrome, infections, inguinal hernia, cutaneous scars (chest tube, patent ductus arteriosus ligation, intravenous infiltration), gastroesophageal reflux, hypertension, craniosynostosis, cholelithiasis, nephrocalcinosis, cutaneous hemangiomas</td>
</tr>
</tbody>
</table>

### PREDICTING NEONATAL MORTALITY

Birthweight and gestational age have traditionally been used as strong indicators for the risk of neonatal death. Indeed, survival at 22 wk of gestation is poor, particularly in those infants requiring aggressive resuscitation in the delivery room. With increasing gestational age, survival rates rise to approximately 15% at 23 wk, 56% at 24 wk, and 79% at 25 wk. The survival of infants of <24 wk gestation, weighing <750 g, and with a 1-min Apgar score <3 is 30%. Antenatal steroids to increase lung maturation, female sex, and singleton pregnancy increase the chance for survival. However, extremely premature infants are also at risk for poor neurodevelopmental outcome.
Birthweight-specific neonatal diseases such as IVH, group B streptococcal sepsis/pneumonia, and pulmonary hypoplasia also contribute to a poor outcome. Scoring systems that have been developed take into consideration physiologic abnormalities (hypotension–hypertension, acidosis, hypoxia, hypercapnia, anemia, neutropenia), as in the Score for Neonate Acute Physiology, or clinical parameters (gestational age, birthweight, anomalies, acidosis, Fio₂), as in the Clinical Risk Index for Babies. The Clinical Risk Index for Babies includes 6 parameters collected in the 1st 12 hr after birth, and the Score for Neonatal Acute Physiology has 26 variables collected in the 1st 24 hr. Prediction models can be used before birth, but additional data from throughout the hospitalization improve the identification of infants at high risk for death or neurodevelopmental impairment. Combining a physician’s judgment and an objective score may produce a more accurate assessment of the risk of death.

**DISCHARGE FROM THE HOSPITAL**

Before discharge, a premature infant should be taking all nutrition by nipple, either bottle or breast (Table 97-9). Some medically fragile infants may be discharged home while receiving gavage feedings after the parents have received appropriate training and education. Growth should be occurring at steady increments of approximately 30 g/day. Temperature should be stable in an open crib. Infants should have had no recent episodes of apnea or bradycardia, and parenteral drug administration should have been discontinued or converted to oral dosing. Stable infants recovering from bronchopulmonary dysplasia may be discharged on a regimen of oxygen given by nasal cannula as long as careful follow-up is arranged with frequent pulse oximetry monitoring and outpatient visits. All infants with birthweight <1,500 g and those with birthweights between 1,500 and 2,000 g with an unstable clinical course requiring oxygen should undergo an eye examination to screen for retinopathy of prematurity. All infants should have a hearing test prior to discharge. In those who had indwelling umbilical arterial catheters, blood pressure should be measured to check for renal vascular hypertension. The hemoglobin level or hematocrit should be determined to evaluate for possible anemia. If all major medical problems have resolved and the home setting is adequate, premature infants may then be discharged when their weight approaches 1,800–2,100 g; close follow-up plus easy access to healthcare providers is essential for early discharge protocols. Alternatively, if the medical or social environment is not ideal, high-risk neonates who have been transported to neonatal intensive care units and whose major illnesses have resolved may be returned to their hospital of birth for an additional period of hospitalization. Standard vaccinations with full doses should commence after discharge or, if infants are still in the hospital, with vaccines that do not contain live viruses. For respiratory syncytial virus prophylaxis, see Chapter 260.

**HOME CARE**

While the infant is in the hospital, the mother should receive instruction on how to care for the baby after discharge and should be allowed to provide infant care in the hospital. Ideally, a home care program should include at least 1 home visit by someone capable of evaluating domestic arrangements and advising about any needed improvements. Early developmental intervention programs focused on parent-infant relationship and/or infant development after discharge improve cognitive development in the short to medium term (up to preschool) but do not improve motor outcomes. However these benefits are not sustained at school age.

**Bibliography is available at Expert Consult.**

### 97.3 Postterm Infants

**Waldemar A. Carlo**

Postterm infants are those born after 42 completed weeks of gestation, as calculated from the mother’s last menstrual period, regardless of weight at birth. Historically, approximately 12% of pregnancies ended after the 294th day. Obstetric interventions often occur earlier, and the rate of postterm births is decreasing. The cause of postterm birth or postmaturity is unknown.

**CLINICAL MANIFESTATIONS**

Postterm infants have normal length and head circumference but may have decreased weight if there is placental insufficiency. Infants born postterm in association with presumed placental insufficiency may have various physical signs. Desquamation, long nails, abundant hair, pale skin, alert faces, and loose skin, especially around the thighs and buttocks, give them the appearance of having recently lost weight; meconium-stained nails, skin, vernix, umbilical cord, and placental membranes may also be noted (see Fig. 88-1 in Chapter 88). Common complications of postmaturity include perinatal depression, meconium aspiration, persistent pulmonary hypertension, hypoglycemia, hypocalcemia, and polycythemia.

**PROGNOSIS**

When delivery is delayed 3 wk or more beyond term, mortality is significantly increased and, in some series, has been approximately 3 times that of a control group of infants born at term. Mortality has been lowered markedly through improved obstetric management.
Bibliography


MANAGEMENT
Careful obstetric monitoring, including nonstress testing, biophysical profile, or Doppler velocimetry, usually provides a rational basis for choosing one of three courses: nonintervention, induction of labor, or cesarean section. Induction of labor or cesarean section may be indicated in older primigravidas more than 2-4 wk beyond term, particularly if evidence of fetal distress is present. Medical problems in the newborn are treated if they arise.

97.4 Large-for-Gestational-Age Infants
Waldemar A. Carlo

See also Chapter 101.1.

Infants with birthweight > the 90th percentile for gestational age are called large for gestational age (LGA). Neonatal mortality rates decrease with increasing birthweight until approximately 4,000 g, after which they increase. These oversized infants are usually born at term, but preterm infants with weights high for gestational age also have a significantly higher mortality than infants of the same size born at term; maternal diabetes and obesity are predisposing factors. Some infants are constitutionally large because of large parental size. LGA infants, regardless of their gestational age, have a higher incidence of birth injuries, such as cervical and brachial plexus injuries, phrenic nerve damage with paralysis of the diaphragm, fractured clavicles, cephalohematomas, subdural hematomas, and ecchymoses of the head and face. LGA infants are also at increased risk for hypoglycemia and polycythemia.

The incidence of congenital anomalies, particularly congenital heart disease, is also higher in LGA infants than in term infants of normal weight. Intellectual and developmental retardation is statistically more common in high birthweight term and preterm infants than in babies of appropriate weight for gestational age.

97.5 Infant Transport
Waldemar A. Carlo

With the advent of regionalized care of high-risk neonates, increasing numbers of high-risk mothers and sick infants are transported to hospitals with neonatal intensive care units. Neonatal transport should include consultation about the infant’s problem and care before transport, ease of access to the transport team, and transport and stabilization by the team before moving the infant. Securing an airway, providing oxygen, assisting with infant ventilation, providing antimicrobial therapy, maintaining the circulation, providing a warmed environment, and placing intravenous or arterial lines or chest tubes should be initiated, if indicated, before transport. Infant and maternal records and laboratory reports should also be provided. Before departure of an infant, the mother should be briefly reassured and allowed to see her stabilized infant; the father should enter his car and follow the transport vehicle to the unit. The transport officer or nurse should also call ahead to inform the receiving unit about the nature of the patient’s illness.

The transport vehicle should be equipped with appropriate medicines, fluids, oxygen tanks, catheters, chest tubes, endotracheal tubes, laryngoscopes, and an infant warming device. It should be well illuminated and have ample room for emergency procedures and monitoring equipment. With efficient transport and appropriately educated nursing and medical staff at the referring hospitals, the mortality of “outborn” neonates should be no higher than that of those born within the tertiary care center.

Bibliography is available at Expert Consult.
Bibliography
The wide varieties of disorders that affect the newborn originate in utero, during birth, or in the immediate postnatal period. These disorders may be caused by prematurity, genetic mutations, chromosomal aberrations, or acquired diseases and injuries. Recognizing disease in newborn infants depends on knowledge of the disorder and evaluation of a limited number of relatively nonspecific clinical signs and symptoms.

Central cyanosis has respiratory, cardiac, central nervous system (CNS), hematologic, and metabolic causes (Table 98-1). Respiratory insufficiency may be a result of pulmonary conditions or may be secondary to CNS depression from drugs, intracranial hemorrhage, or anoxia. If respiratory insufficiency is caused by pulmonary conditions, respirations tend to be rapid and may be accompanied by retraction of the thoracic cage. If it is caused by the CNS depression, respirations tend to be irregular and weak and are often slow. Cyanosis unaccompanied by obvious signs of respiratory difficulty suggests cyanotic congenital heart disease or methemoglobinemia. Cyanosis resulting from congenital heart disease may, however, be difficult to distinguish clinically from cyanosis caused by respiratory disease. Episodes of cyanosis may also be the initial sign of hypoglycemia, bacteremia, meningitis, shock, or pulmonary hypertension. Peripheral acrocyanosis is common in neonates and does not usually warrant concern unless poor perfusion is suspected.

Pallor, in addition to anemia or acute hemorrhage, should suggest hypoxia, asphyxia, hypoglycemia, sepsis, shock, or adrenal failure.

Hypotension in term infants suggests shock from hypovolemia (hemorrhage, dehydration), the systemic inflammatory response syndrome (bacterial sepsis, intrauterine infection, necrotizing enterocolitis), cardiac dysfunction (left heart obstructive lesions—hypoplastic left-heart syndrome, myocarditis, asphyxia-induced myocardial stunning, anomalous coronary artery), pneumothorax, pneumopericardium, pericardial effusion, or metabolic disorders (hypoglycemia, adrenal insufficiency—salt-losing adrenogenital syndrome). Hypotension is a common problem in sick preterm infants and may also be caused by any of the problems noted in a term infant. Hypotension may develop in preterm infants with severe respiratory distress syndrome. Strategies used to support blood pressure include volume expansion (normal saline is equally as effective as 5% albumin), pressors (dopamine, dobutamine, epinephrine, norepinephrine, vasopressin), and corticosteroids. Hypotension in some infants weighing <1,000 g does not respond to fluids or inotropic agents but may respond to therapy with intravenous hydrocortisone. Sudden onset of hypotension in a very-low birthweight infant suggests pneumothorax, intraventricular hemorrhage, or subcapsular hepatic hematoma.

Seizures (see Chapter 593.7) usually point to a disorder of the CNS and suggest hypoxic–ischemic encephalopathy, intracranial hemorrhage, cerebral anomaly, subdural effusion, meningitis, hypocalcemia, hypoglycemia, cerebral infarction, benign familial seizures, or, rarely, pyridoxine dependence, hyponatremia, hypernatremia, inborn errors of metabolism, or drug withdrawal. Seizures beginning in the delivery room or shortly thereafter may be the result of the unintentional injection of maternal local anesthetic into the fetus. Seizures may also result from hyponatremia and water intoxication in the infant after the administration of large amounts of hypotonic fluid to the mother shortly before and during delivery.
Table 98-1  Differential Diagnosis of Cyanosis in the Newborn

<table>
<thead>
<tr>
<th>CENTRAL OR PERIPHERAL NERVOUS SYSTEM HYPOVENTILATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth asphyxia</td>
</tr>
<tr>
<td>Intracranial hypertension, hemorrhage</td>
</tr>
<tr>
<td>Oversedation (direct or through maternal route)</td>
</tr>
<tr>
<td>Diaphragm palsy</td>
</tr>
<tr>
<td>Neuromuscular diseases</td>
</tr>
<tr>
<td>Seizures</td>
</tr>
<tr>
<td>RESPIRATORY DISEASE</td>
</tr>
<tr>
<td>Airway</td>
</tr>
<tr>
<td>Choanal atresia/stenosis</td>
</tr>
<tr>
<td>Pierre Robin syndrome</td>
</tr>
<tr>
<td>Intrinsic airway obstruction (laryngeal/bronchial/tracheal stenosis)</td>
</tr>
<tr>
<td>Extrinsic airway obstruction (bronchogenic cyst, duplication cyst, vascular compression)</td>
</tr>
<tr>
<td>Lung</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
</tr>
<tr>
<td>Transient tachypnea</td>
</tr>
<tr>
<td>Meconium aspiration</td>
</tr>
<tr>
<td>Pneumonia (sepsis)</td>
</tr>
<tr>
<td>Pneumothorax</td>
</tr>
<tr>
<td>Congenital diaphragmatic hemia</td>
</tr>
<tr>
<td>Pulmonary hypoplasia</td>
</tr>
<tr>
<td>CARDIAC RIGHT-TO-LEFT SHUNT</td>
</tr>
<tr>
<td>Abnormal connections (pulmonary blood flow normal or increased)</td>
</tr>
<tr>
<td>Transposition of great vessels</td>
</tr>
<tr>
<td>Total anomalous pulmonary venous return</td>
</tr>
<tr>
<td>Truncus arteriosus</td>
</tr>
<tr>
<td>Hypoplastic left heart syndrome</td>
</tr>
<tr>
<td>Single ventricle or tricuspid atresia with large ventricular septal defect but without pulmonic stenosis</td>
</tr>
<tr>
<td>Obstructed pulmonary blood flow (pulmonary blood flow decreased)</td>
</tr>
<tr>
<td>Pulmonary atresia with intact ventricular septum</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
</tr>
<tr>
<td>Critical pulmonic stenosis with patent foramen ovale or atrial septal defect</td>
</tr>
<tr>
<td>Tricuspid atresia</td>
</tr>
<tr>
<td>Single ventricle with pulmonic stenosis</td>
</tr>
<tr>
<td>Ebstein malformation of the tricuspid valve</td>
</tr>
<tr>
<td>Persistent fetal circulation (persistent pulmonary hypertension of newborn)</td>
</tr>
<tr>
<td>METHEMOGLOBINEMIA</td>
</tr>
<tr>
<td>Congenital (hemoglobin M, methemoglobin reductase deficiency)</td>
</tr>
<tr>
<td>Acquired (nitrates, nitrites)</td>
</tr>
<tr>
<td>Inadequate ambient O₂ or less O₂ delivered than expected (rare)</td>
</tr>
<tr>
<td>Disconnection of O₂ supply to nasal cannula, head hood</td>
</tr>
<tr>
<td>Connection of air, rather than O₂, to a mechanical ventilator</td>
</tr>
<tr>
<td>SPURIOUS/ARTIFACTUAL</td>
</tr>
<tr>
<td>Oximeter artifact (poor contact between probe and skin, poor pulse searching)</td>
</tr>
<tr>
<td>Arterial blood gas artifact (contamination with venous blood)</td>
</tr>
<tr>
<td>OTHER</td>
</tr>
<tr>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Adrenogenital syndrome</td>
</tr>
<tr>
<td>Polycythemia</td>
</tr>
<tr>
<td>BLOOD LOSS</td>
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</tbody>
</table>


Seizures should be distinguished from the jitteriness that may be present in normal newborns, in infants of diabetic mothers, in those who experienced birth asphyxia or drug withdrawal, and in polycythemic infants. An examiner may stop the jitteriness resembling simple tremors by holding the infant's extremity; this jitteriness often depends on sensory stimuli and occurs when the infant is active, and it is not associated with abnormal eye movements. Tremors are often more rapid with a smaller amplitude than those of tonic-clonic seizures.

Seizures in premature infants are often subtle and associated with abnormal eye (fluttering, deviation, stare) or facial (chewing, tongue thrusting) movements; the motor component is often that of tonic extension of the limbs, neck, and trunk. Term infants may have focal or multifocal, clonic or myoclonic movements, but they may also have more subtle seizure activity. Apnea may be the first manifestation of seizure activity, particularly in a premature infant. Seizures may adversely affect the subsequent neurodevelopmental outcome and may even predispose an infant to nonneonatal seizures. Seizures should be treated aggressively.

After severe birth asphyxia, infants may have motor automatisms characterized by oral-buccal-lingual movements, rotary limb activities (rowing, pedaling, swimming), tonic posturing, or myoclonus. These motor activities are not usually accompanied by time-synchronized electroencephalographic discharges, may not signify cortical epileptic activity, respond poorly to anticonvulsant therapy, and are associated with a poor prognosis. Such automatisms may represent cortical depression that produces a brainstem release phenomenon or subcortical seizures.

Lethargy may be a manifestation of infection, asphyxia, hypoglycemia, hypercapnia, sedation from maternal analgesia or anesthesia, a cerebral defect, or, indeed, almost any severe disease, including an inborn error of metabolism. Lethargy appearing after the 2nd day should, in particular, suggest infection. Lethargy with emesis suggests increased intracranial pressure or an inborn error of metabolism.

Irritability may be a sign of discomfort accompanying intraabdominal conditions, meningeval irritation, drug withdrawal, infections, congenital glaucoma, or any condition producing pain. As in later infancy, the eardrums should always be examined as a possible source of pain. Hyperactivity, especially in a premature infant, may be a sign of hypoxia, pneumothorax, emphysema, hypoglycemia, hypocalcemia, CNS damage, drug withdrawal, neonatal thyrotoxicosis, bronchospasm, esophageal reflex, or discomfort from a cold environment.

Failure to feed well is seen in most sick newborn infants and should lead a careful search for infection, a central or peripheral nervous system disorder, intestinal obstruction, and other abnormal conditions.

Fever may be the result of too high an environmental temperature because of weather, overheated nurseries or incubators/radiant warmers, or too many clothes. It is also noted in "dehydration fever" of newborn infants. If these causes of fever can be eliminated, serious infection (pneumonia, bacteremia, meningitis, and viral infections, particularly herpes simplex or enteroviruses) must be considered, although such infections often occur without provoking a febrile response in newborn infants (see Chapters 176 and 177). Unexplained hypothermia may accompany infection or other serious disturbances of the circulation or CNS. A sudden servocontrolled increase in incubator ambient temperature to maintain body temperature is a sign of temperature instability and may be associated with sepsis or any of the conditions already mentioned.

Periods of apnea, particularly in premature infants, may be associated with various disturbances (see Chapter 101.2). When apnea recurs, or when the intervals are longer than 20 sec, or are associated with cyanosis or bradycardia, an immediate diagnostic evaluation is needed.

Jaundice during the 1st 24 hr of life warrants diagnostic evaluation and should be considered to be due to hemolysis until proven otherwise. Septicemia and intrauterine infections, such as syphilis, cytomegalovirus, and toxoplasmosis, should also be considered, especially in infants with an increase in direct bilirubin value.

Jaundice after the 1st 24 hr may be "physiologic" or may be caused by septicemia, hemolytic anemia, galactosemia, hepatitis, congenital atresia of the bile ducts, inspissated bile syndrome after erythroblastosis fetalis, syphilis, herpes simplex, other congenital infections, or other conditions (see Chapter 102.3).

Vomiting during the 1st day of life suggests obstruction in the upper digestive tract or increased intracranial pressure. Roentgenographic studies are indicated when obstruction is suspected. Vomiting may also be a nonspecific symptom of an illness such as septicemia. It is a common manifestation of overfeeding, inexperienced feeding technique, or normal reflux and is rarely caused by pyloric stenosis, milk allergy, duodenal ulcer, stress ulcer, an inborn error of metabolism.
Common Life-Threatening Congenital Anomalies

Pain in the Neonate: General Considerations

- Pain in newborns is often unrecognized and/or undertreated.
- If a procedure is painful in adults, it should be considered painful in newborns.
- Healthcare institutions should develop and implement patient care policies to assess, prevent, and manage pain in neonates.
- Pharmacologic agents with known pharmacokinetic and pharmacodynamic properties and demonstrated efficacy in neonates should be used. Agents known to compromise cardiorespiratory function should be administered only by persons experienced in neonatal airway management and in settings with the capacity for continuous monitoring.
- Educational programs to increase the skills of healthcare professionals in the assessment and management of stress and pain in neonates should be provided.
- Further research is needed to develop and validate neonatal pain assessment tools that are useful in the clinical setting; to determine optimal behavioral and pharmacologic interventions; and to study long-term effects of pain and pain management.


Table 98-2

<table>
<thead>
<tr>
<th>NAME</th>
<th>MANIFESTATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choanal atresia</td>
<td>Respiratory distress in delivery room, nasogastric tube cannot be passed through nares</td>
</tr>
<tr>
<td>Pierre Robin syndrome</td>
<td>Suspect CHARGE (coloboma of the eye, heart anomaly, choanal atresia, retardation, and genital and ear anomalies) syndrome</td>
</tr>
<tr>
<td>Stickler syndrome</td>
<td>Micrognathia, cleft palate, airway obstruction</td>
</tr>
<tr>
<td>Diaphragmatic hernia</td>
<td>Scaphoid abdomen, bowel sounds present in chest, respiratory distress</td>
</tr>
<tr>
<td>Tracheoesophageal fistula</td>
<td>Polyhydramnios, aspiration pneumonia, excessive salivation, nasogastric tube cannot be placed in stomach</td>
</tr>
<tr>
<td>Intestinal obstruction: volvulus, duodenal atresia</td>
<td>Polyhydramnios, bile-stained emesis, abdominal distention</td>
</tr>
<tr>
<td>Intestinal obstruction: ileal atresia</td>
<td>Suspect trisomy 21, cystic fibrosis, cocaine, malrotation</td>
</tr>
<tr>
<td>Gastrochisis, omphalocele</td>
<td>Polyhydramnios, intestinal obstruction</td>
</tr>
<tr>
<td>Renal agenesis, Potter syndrome</td>
<td>Polyhydramnios, anuria, pulmonary hypoplasia, pneumothorax</td>
</tr>
<tr>
<td>Neural tube defects: anencephalus, meningomyelocele</td>
<td>Polyhydramnios, elevated α-fetoprotein, decreased fetal activity</td>
</tr>
<tr>
<td>Ductus-dependent congenital heart disease</td>
<td>Cyanosis, hypotension, murmur</td>
</tr>
</tbody>
</table>

(hyperammonemia, metabolic acidosis), or adrenal insufficiency. Vomitus containing dark blood is usually a sign of a serious illness; the benign possibility of swallowed maternal blood should also be considered. Bile-stained vomitus strongly suggests obstruction below the ampulla of Vater and warrants contrast-enhanced radiography in many cases.

Diarrhea may be a symptom of overfeeding (especially high-caloric density formula), acute gastroenteritis, or malabsorption, or it may be a nonspecific symptom of infection. Diarrhea may occur in conditions accompanied by compromised circulation of part of the intestinal or genital tract, such as mesentric thrombosis, necrotizing enterocolitis, strangled hernia, intussusception, and torsion of the ovary or testis.

Abdominal distention, usually a sign of intestinal obstruction or an intraabdominal mass, may also be seen in infants with enteritis, necrotizing enterocolitis, isolated intestinal perforation, ileus accompanying sepsis, respiratory distress, ascites, or hypokalemia.

Failure to move an extremity (pseudoparalysis) suggests fracture, dislocation, or nerve injury. It is also seen in osteomyelitis and other infections that cause pain on movement of the affected part.

Pain in neonates may be unrecognized and/or undertreated. The intensive care of neonates may involve a number of painful procedures, including blood sampling (heelstick, venous or arterial puncture), endotracheal intubation and suctioning, mechanical ventilation, and insertion of chest tubes and intravascular catheters. Pain in neonates results in obvious distress and acute physiologic stress responses, which may have developmental implications for pain in later life. Moreover, the knowledge that infants may experience pain contributes to the stress of parents of sick newborns.

Pain and discomfort are potentially avoidable problems during the treatment of sick infants. Preemptive relief from painful stimuli should be provided before pain or anxiety develops. The most frequently used drugs are intermittent or continuous doses of opioids (morphine, fentanyl) and benzodiazepines (midazolam, lorazepam). Although the long-term effects of opioids and sedatives are not well established, the first concern should be the treatment and/or prevention of acute pain. Continuous opiate infusions should be used with caution. Some minor but painful procedures performed in well neonates can be managed with oral sucrose solutions (Table 98-2).

CONGENITAL ANOMALIES

Congenital anomalies are a major cause of stillbirths and neonatal deaths. In the United States and other developed countries, congenital anomalies are one of the main causes of neonatal mortality. In addition, congenital anomalies are a major cause of acute illness and long-term morbidity. Anomalies are discussed in general in Chapters 81 and 108, and specifically in the chapters on the various systems of the body. Early recognition of anomalies is important for planning care; with some, such as congenital heart disease, tracheoesophageal fistula, diaphragmatic hernia, choanal atresia, and intestinal obstruction, immediate medical and/or surgical therapy is essential for survival (Table 98-3). Parents are likely to feel anxious and guilty upon learning of the existence of a congenital anomaly and require sensitive counseling.

Bibliography is available at Expert Consult.
Bibliography


Chapter 99
Nervous System Disorders

Waldemar A. Carlo and Namasivayam Ambalavanan

Central nervous system (CNS) disorders are important causes of neonatal mortality and both short- and long-term morbidity. The CNS can be damaged as a result of asphyxia, hemorrhage, trauma, hypoglycemia, or direct cytotoxicity. The etiology of CNS damage is often multifactorial and includes perinatal complications, postnatal hemodynamic instability, and developmental abnormalities that may be genetic and/or environmental. Predisposing factors for brain injury include chronic and acute maternal illness resulting in uteroplacental dysfunction, intrauterine infection, macrosomia/dystocia, malpresentation, prematurity, and intrauterine growth restriction. Acute and often unavoidable emergencies during the delivery process sometimes result in mechanical and/or hypoxic–ischemic brain injury.

99.1 The Cranium

Waldemar A. Carlo and Namasivayam Ambalavanan

Erythema, abrasions, ecchymoses, and subcutaneous fat necrosis of facial or scalp soft tissues may be noted after a normal delivery or after forceps or vacuum-assisted deliveries. Their location depends on the area of contact with the pelvic bones or of application of the forceps. Traumatic hemorrhage may involve any layer of the scalp as well as intracranial contents (Fig. 99-1).

Caput succedaneum is a diffuse, sometimes ecchymotic, edematous swelling of the soft tissues of the scalp involving the area presenting during vertex delivery (see Fig. 99-1). It may extend across the midline and across suture lines. The edema disappears within the 1st few days of life. Molding of the head and overriding of the parietal bones are frequently associated with caput succedaneum and become more evident after the caput has receded; they disappear during the 1st few wk of life. Rarely, a hemorrhagic caput may result in shock and require blood transfusion. Analogous swelling, discoloration, and distortion of the face are seen in face presentations. No specific treatment is needed, but if extensive ecchymoses are present, hyperbilirubinemia may develop.

Cephalohematoma (Fig. 99-2) is a subperiosteal hemorrhage, hence always limited to the surface of 1 cranial bone. Cephalohematomas occur in 1-2% of live births. No discoloration of the overlying scalp occurs, and swelling is not usually visible for several hours after birth because subperiosteal bleeding is a slow process. The lesion becomes a firm tense mass with a palpable rim localized over 1 area of the skull. Most cephalohematomas are resorbed within 2 wk-3 mo, depending on their size. They may begin to calcify by the end of the 2nd wk. A few remain for years as bony protuberances and are detectable on radiographs as widening of the diploic space; cystlike defects may persist for months or years. An underlying skull fracture, usually linear and not depressed, may be associated with 10-25% of cases. A sensation of central depression suggesting but not indicative of an underlying fracture or bony defect is usually encountered on palpation of the organized rim of a cephalohematoma. Cephalohematomas require no treatment, although phototherapy may be necessary to treat hyperbilirubinemia. Infection of the hematoma is a very rare complication.

A subgaleal hemorrhage is a collection of blood beneath the aponeurosis that covers the scalp and serves as the insertion for the occipitofrontalis muscle. Bleeding can be very extensive into this large potential space and may even dissect into the subcutaneous tissues of the neck. There is often an association with vacuum-assisted delivery. The mechanism of injury is most likely secondary to rupture of emissary veins connecting the dural sinuses within the skull with the superficial veins of the scalp, sometimes associated with skull fractures, suture diastasis, and fragmentation of the superior margin of the parietal bone. Extensive subgaleal bleeding is occasionally secondary to a hereditary coagulopathy (hemophilia). A subgaleal hemorrhage manifests as a fluctuating mass that straddles cranial sutures or fontanelles that increases in size after birth. Some patients have a consumptive coagulopathy owing to massive blood loss. Patients should be monitored for hypotension, anemia, and the development of hyperbilirubinemia. These lesions typically resolve over 2-3 wk.

Fractures of the skull may occur as a result of pressure from forceps or from the maternal symphys symphysis pubis, sacral promontory, or ischial spines. Linear fractures, the most common, cause no symptoms and require no treatment. Depressed fractures are usually indentations of the calvaria similar to the dents in a ping-pong ball; they are generally a complication of forceps delivery or fetal compression. Affected infants may be asymptomatic unless they have associated intracranial injury; it is advisable to elevate severe depressions to prevent cortical injury from sustained pressure. Although some may elevate spontaneously, some require treatment. Percutaneous microscrew elevation is one method successfully used to elevate depressed skull fractures. Fracture of the occipital bone with separation of the basal and squamous portions frequently causes fatal hemorrhage because of disruption of the underlying vascular sinuses. Such fractures may result in haemorrhage, subdural hematoma, and underlying neurological deficits.

Figure 99-1 Sites of extracranial (and extradural) hemorrhages in the newborn. Schematic diagram of important tissue planes from skin to dura. (From Volpe JJ: Neurology of the newborn, ed 4, Philadelphia, 2001, WB Saunders.)

Figure 99-2 Cephalohematoma of the right parietal bone.
during breech deliveries from traction on the hyperextended spine of the infant while the head is fixed in the maternal pelvis. Subconjunctival and retinal hemorrhages are frequent; petechiae of the skin of the head and neck are also common. All are probably secondary to a sudden increase in intrathoracic pressure during passage of the chest through the birth canal. Parents should be assured that these hemorrhages are temporary and the result of normal events of delivery. The lesions resolve rapidly within the 1st 2 wk of life.

**99.2 Traumatic, Epidural, Subdural, and Subarachnoid Hemorrhage**

Waldemar A. Carlo and Namasivayam Ambalavanan

Traumatic epidural, subdural, or subarachnoid hemorrhage is especially likely when the fetal head is large in proportion to the size of the mother's pelvic outlet, with prolonged labor, in breech or precipitous deliveries, or as a result of mechanical assistance with delivery. Asymptomatic subdural hemorrhage may be noted within 48 hr of birth after vaginal or cesarean delivery. Massive subdural hemorrhage, often associated with tears in the tentorium cerebelli or, less frequently, in the falx cerebri, is rare but is encountered more often in full-term than in premature infants. Patients with massive hemorrhage caused by tears of the tentorium or falx cerebri rapidly deteriorate and may die soon after birth. The majority of subdural and epidural hemorrhages resolve without intervention; consultation with a neurosurgeon is recommended. The diagnosis of subdural hemorrhage may be delayed until the chronic subdural fluid volume expands and produces mega-locephaly, frontal bossing, a bulging fontanel, anemia, and, sometimes, seizures. CT scan and MRI are useful imaging techniques to confirm these diagnoses. Symptomatic subdural hemorrhage in large term infants should be treated by removal of the subdural fluid collection with a needle placed through the lateral margin of the anterior fontanel. In addition to birth trauma, child abuse must be suspected in all infants with subdural effusion after the immediate neonatal period; asymptomatic subdural hemorrhages following labor should resolve by 4 wk of age.

Subarachnoid hemorrhage is rare and typically is clinically silent. The anastomoses between the penetrating leptomeningeal arteries or the bridging veins are the most likely source of the bleeding. The majority of affected infants have no clinical symptoms, but the subarachnoid hemorrhage may be detected because of an elevated number of red blood cells in a lumbar puncture sample. Some infants experience benign seizures, which tend to occur on the 2nd day of life. Rarely, an infant has a life-threatening catastrophic hemorrhage and dies. There are usually no neurologic abnormalities during the acute episode or on follow-up. Significant neurologic findings should suggest an arteriovenous malformation; this lesion can easily be detected on CT or MRI; ultrasonography is a less-sensitive tool.

**99.3 Intracranial–Intraventricular Hemorrhage and Periventricular Leukomalacia**

Waldemar A. Carlo and Namasivayam Ambalavanan

**ETIOLOGY**

Intracranial hemorrhage usually develops spontaneously; less commonly, it may be caused by trauma or asphyxia, and rarely, it occurs from a primary hemorrhagic disturbance or congenital vascular anomaly. Intracranial hemorrhage often involves the ventricles (intraventricular hemorrhage [IVH]) of premature infants delivered spontaneously without apparent trauma. Primary hemorrhagic disturbances and vascular malformations are rare and usually give rise to subarachnoid or intracerebral hemorrhage. In utero hemorrhage associated with maternal idiopathic or, more often, fetal alloimmune thrombocytopenia may occur as severe cerebral hemorrhage or a porencephalic cyst after resolution of a fetal cortical hemorrhage. Intracranial bleeding may be associated with disseminated intravascular coagulopathy, isoimmune thrombocytopenia, and neonatal vitamin K deficiency, especially in infants born to mothers receiving phenobarbital or phenytoin.

**EPIDEMIOLOGY**

The overall incidence of IVH has decreased over the past decades as a result of improved perinatal care and increased use of antenatal corticosteroids, surfactant to treat respiratory distress syndrome (RDS), and, possibly; prophylactic indomethacin; however, it continues to be an important cause of morbidity in preterm infants. Approximately 30% of premature infants <1,500 g have IVH. The risk is inversely related to gestational age and birthweight, with the smallest and most immature infants being at the highest risk; 7% of infants weighing 1,001-1,500 g have a severe IVH (grade III or IV), compared with 14% of infants weighing 751-1,000 g and 24% of infants weighing ≤750 g. In 3% of infants weighing <1,000 g, periventricular leukomalacia (PVL) develops.

**PATHOGENESIS**

The major neuropathologic lesions associated with very-low-birthweight (VLBW) infants are IVH and PVL. IVH in premature infants occurs in the gelatinous subependymal germinal matrix. This periven-tricular area is the site of origin for embryonal neurons and fetal glial cells, which migrate outwardly to the cortex. Immature blood vessels in this highly vascular region of the developing brain combined with poor tissue vascular support predispose premature infants to hemorrhage. The germinal matrix involutes as the infant approaches full-term gestation and the tissue's vascular integrity improves; therefore IVH is much less common in the term infant. Periventricular hemorrhagic infarction often develops after a large IVH owing to venous congestion. Predisposing factors for IVH include prematurity, RDS, hypoxic–ischemic or hypotensive injury, reperfusion injury of damaged vessels, increased or decreased cerebral blood flow, reduced vascular integrity, increased venous pressure, pneumothorax, thrombocytopenia, hypervolemia, and hypertension.

Understanding of the pathogenesis of PVL is evolving, and it appears to involve both intrauterine and postnatal events. A complex interaction exists between the development of the cerebral vasculature and the regulation of cerebral blood flow (both of which are gestational age-dependent), disturbances in the oligodendrocyte precursors required for myelination, and maternal/fetal infection and/or inflam-mation. Similar factors (hypoxia–ischemia), venous obstruction from an IVH, or undetected fetal stress may result in decreased perfusion to the brain, leading, in turn, to periventricular hemorrhage and necrosis. PVL is characterized by focal necrotic lesions in the periventricular white matter and/or more diffuse white matter damage. The risk for PVL increases in infants with severe IVH and/or ventriculomegaly. The corticospinal tracts descend through the periventricular white matter, hence the association between cerebral white matter injury/PVL and motor abnormalities, including cerebral palsy.

**CLINICAL MANIFESTATIONS**

The majority of patients with IVH, including some with moderate to severe hemorrhages, have no initial clinical signs. Some premature infants in whom severe IVH develops may have acute deterioration on the 2nd or 3rd day of life. Hypotension, apnea, pallor, or cyanosis; poor suck; abnormal eye signs; a high-pitched, shrill cry; convulsions, or decreased muscle tone; metabolic acidosis; shock; and a decreased hematocrit or failure of the hematocrit to increase after transfusion may be the first clinical indications. IVH may rarely manifest at birth; 50% of cases are diagnosed within the 1st day of life, and up to 75% within the 1st 3 days. A small percentage of infants have late hemorrhage, between days 14 and 30. IVH as a primary event is rare after the 1st mo of life.

PVL is usually clinically asymptomatic until the neurologic sequelae of white matter damage become apparent in later infancy as spastic motor deficits. PVL may be present at birth but usually occurs later as
an early echodense phase (3–10 days of life), followed by the typical echolucent (cystic) phase (14–20 days of life).

The severity of hemorrhage may be defined on cranial imaging by the location and degree of bleeding and ventricular dilation. In a grade I hemorrhage, bleeding is isolated to the subependymal area. In Grade II hemorrhage, there is bleeding within the ventricle but without evidence of ventricular dilation. Grade III hemorrhage consists of IVH with ventricular dilation. In Grade IV hemorrhage, there is intraventricular and parenchymal hemorrhage. Another grading system describes 3 levels of increasing severity of IVH detected on ultrasound: In grade I, bleeding is confined to the germinal matrix–subependymal region or to <10% of the ventricle (~35% of IVH cases); grade II is defined as intraventricular bleeding with 10–50% filling of the ventricle (~40% of IVH cases) and in grade III, more than 50% of the ventricle is involved, with dilated ventricles (Fig. 99-3). Ventriculomegaly is defined as mild (0.5–1 cm dilation), moderate (1.0–1.5 cm dilation), or severe (>1.5 cm dilation).

**DIAGNOSIS**

Intracranial hemorrhage is suspected on the basis of the history, clinical manifestations, and knowledge of the birthweight–specific risks for IVH. The associated clinical signs of IVH are typically nonspecific or absent; therefore, it is recommended that premature infants <32 wk of gestation be evaluated with routine real-time cranial ultrasonography through the anterior fontanel to screen for IVH. Infants <1,000 g are at highest risk and should undergo cranial ultrasonography within the 1st 3–7 days of age, when approximately 75% of lesions will be detectable. Ultrasonography is the preferred imaging technique for screening because it is noninvasive, portable, reproducible, and sensitive and specific for detection of IVH. All at-risk infants should undergo follow-up ultrasonography at 36–40 wk of postmenstrual age to evaluate adequately for PVL, because cystic changes related to perinatal injury may not be visible for at least 2–4 wk. In one study, 29% of low-birthweight (LBW) infants who later experienced cerebral palsy did not have radiographic evidence of PVL until after 28 days of age. Ultrasonography also detects the precystic and cystic symmetric lesions of PVL and the asymmetric intraparenchymal echogenic lesions of cortical hemorrhagic infarction. Furthermore, the delayed development of cortical atrophy, porencephaly, and the severity, progression, or regression of posthemorrhagic hydrocephalus can be determined by serial ultrasonographic examinations.

Approximately 3–5% of VLBW infants develop posthemorrhagic hydrocephalus (PHH) that sometimes requires ventriculoperitoneal shunt insertion; if the initial ultrasonographic findings are abnormal, additional interval ultrasonographic studies are indicated to monitor for the development of hydrocephalus.

IVH represents only 1 facet of brain injury in the term or preterm infant. MRI is a more sensitive tool for evaluation of extensive periventricular injury and may be more predictive of adverse long-term outcome. CT or, more reliably, diffusion-weighted MRI is indicated for term infants in whom brain injury or stroke is suspected, because ultrasonography may not reveal edema or intraparenchymal hemorrhage and infarction.

**PROGNOSIS**

The degree of IVH and the presence of PVL are strongly linked to neurodevelopmental impairment. For infants with a birthweight of <1,000 g, the incidences of severe neurologic impairment (defined as Bayley Scales of Infant Development II mental developmental index <70, psychomotor development index <70, cerebral palsy, blindness, or deafness) are approximately 50%, 55%, and 70% for infants with grade II, grade III, and grade IV IVH, respectively (Table 99-1). In contrast, the rate of neurodevelopmental impairment is approximately 40% in infants (weighing <1,000 g) without IVH and those with grade I IVH. PVL, cystic PVL, and progressive hydrocephalus requiring shunt insertion are each independently associated with a poorer prognosis.

Most infants with IVH and acute ventricular distention do not have PHH. Ten percent to 15% of LBW neonates with IVH demonstrate PHH, which may initially be present without clinical signs, such as an enlarging head circumference, lethargy, a bulging fontanel or widely split sutures, apnea, and bradycardia. In infants in whom symptomatic hydrocephalus develops, clinical signs may be delayed 2–4 wk despite progressive ventricular distention with compression and thinning of the cerebral cortex. Many infants with PHH have spontaneous regression; 3–5% of VLBW infants with PHH require shunt insertion. Infants with PHH requiring shunt insertion have lower cognitive and psychomotor performance at 18–22 mo.

**PREVENTION**

Improved perinatal care is imperative to minimize traumatic brain injury and decrease the risk of preterm delivery. The incidence of traumatic intracranial hemorrhage may be reduced by judicious management of cephalopelvic disproportion and operative (forceps, vacuum) delivery. Fetal or neonatal hemorrhage caused by maternal idiopathic thrombocytopenic purpura or alloimmune thrombocytopenia may be reduced by maternal treatment with steroids, intravenous immunoglobulin, fetal platelet transfusion, or cesarean section. Metabolic care of the LBW infant’s respiratory status and fluid and electrolyte management—including avoidance of acidosis, hypocarbia, hypoxia, hypotension, wide fluctuations in neonatal blood pressure or PCO₂, and pneumothorax—are important factors that may affect the risk for development of IVH and PVL.

A single course of antenatal corticosteroids is recommended in pregnancies 24–34 wk of gestation that are at risk for preterm delivery. Antenatal steroids decrease the risk of death, grades III and IV IVH,
Table 99-1

<table>
<thead>
<tr>
<th>HEAD ULTRASOUND VARIABLE</th>
<th>NDI</th>
<th>MDI &gt; 70</th>
<th>PDI &lt; 70</th>
<th>CEREBRAL PALSY</th>
<th>BLINDNESS</th>
<th>DEAFNESS</th>
<th>NONINDEPENDENT WALKING</th>
<th>NONINDEPENDENT FEEDING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (n = 1308)</td>
<td>39.4</td>
<td>31.9</td>
<td>18.8</td>
<td>10.1</td>
<td>1.6</td>
<td>1.5</td>
<td>7.7</td>
<td>12.8</td>
</tr>
<tr>
<td>Intracranial hemorrhage:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 (n = 244)</td>
<td>40.6</td>
<td>31.5</td>
<td>18.0</td>
<td>17.2</td>
<td>2.9</td>
<td>1.2</td>
<td>10.7</td>
<td>13.9</td>
</tr>
<tr>
<td>Grade 2 (n = 151)</td>
<td>51.0</td>
<td>36.9</td>
<td>22.3</td>
<td>17.2</td>
<td>4.0</td>
<td>3.3</td>
<td>9.3</td>
<td>13.9</td>
</tr>
<tr>
<td>Grade 3 (n = 215)</td>
<td>55.4</td>
<td>43.3</td>
<td>36.7</td>
<td>31.3</td>
<td>7.0</td>
<td>2.8</td>
<td>25.1</td>
<td>23.4</td>
</tr>
<tr>
<td>Grade 4 (n = 145)</td>
<td>69.7</td>
<td>52.6</td>
<td>55.5</td>
<td>51.4</td>
<td>11.2</td>
<td>4.9</td>
<td>42.4</td>
<td>28.5</td>
</tr>
<tr>
<td>Periventricular leukomalacia (n = 134)</td>
<td>72.4</td>
<td>60.3</td>
<td>52.8</td>
<td>50.0</td>
<td>10.5</td>
<td>3.7</td>
<td>44.0</td>
<td>29.1</td>
</tr>
<tr>
<td>Cystic periventricular leukomalacia (n = 50)</td>
<td>76.0</td>
<td>60.4</td>
<td>64.6</td>
<td>64.0</td>
<td>18.0</td>
<td>6.3</td>
<td>50.0</td>
<td>32.0</td>
</tr>
</tbody>
</table>

*All infants were counted only once and were assigned the highest grade of intracranial hemorrhage/leukomalacia from either head ultrasound scan. Missing values in either the row or column variable were excluded from the analysis.

MDI, Mental Developmental Index; NDI, neurodevelopment impairment; PDI, Psychomotor Developmental Index.


and PVL in the neonate. The prophylactic administration of low-dose indomethacin (0.1 mg/kg/day for 3 days) to VLBW preterm infants reduces the incidence of severe IVH.

**TREATMENT**

Although no treatment is available for IVH, it may be associated with other complications that require therapy. Seizures should be treated with anticonvulsant drugs. Anemia and coagulopathy require transfusion with packed red blood cells or fresh-frozen plasma. Shock and acidosis are treated with the judicious and slow administration of sodium bicarbonate and fluid resuscitation.

Insertion of a ventriculoperitoneal shunt is the preferred method to treat progressive and symptomatic PHH; some infants require temporary cerebrospinal fluid diversion before a permanent shunt can be safely inserted. Diuretics and acetazolamide are not effective.

Serial lumbar punctures, ventricular taps or reservoirs, and externalized ventricular drains are potential temporizing interventions; they have an associated risk of infection and of “puncture porencephaly” owing to injury to the surrounding parenchyma. A ventriculosubgaleal shunt inserted from the ventricle into a surgically created subgaleal pocket provides a closed system for constant ventricular decompression without these additional risk factors. Decompression is regulated by the pressure gradient between the ventricle and the subgaleal pocket.

Bibliography is available at Expert Consult.

**99.4 Brain Injury from Inflammation, Infection, and Medications**

Waldemar A. Carlo and Namasivayam Ambalavanan

Severe IVH and PVL are the most commonly associated risk factors for adverse outcome in the VLBW infant. Other factors are also involved in the etiology of perinatal brain injury. Cytokines and prenatal or postnatal infection or inflammation may contribute to brain injury. A systemic inflammatory response syndrome in the mother, fetus, or infant may induce the production of various inflammatory mediators that are directly cytotoxic or cause decreased CNS perfusion (Fig. 99-4). Preterm infants with evidence (often subclinical) of intrauterine or postnatal infection or maternal chorioamnionitis are more likely than uninfected infants to have adverse neurodevelopmental outcome including cerebral palsy.

In utero infections may involve the developing CNS and directly impair cell growth or produce cell neurosis, resulting in microcephaly, developmental delay, mental retardation, or cerebral palsy. These specific congenital or perinatal acquired infections include those caused by cytomegalovirus (see Chapter 255), toxoplasmosis (see Chapter 99.4).
Bibliography
Hypoxic–Ischemic Encephalopathy

99.5 Hypoxic–Ischemic Encephalopathy

Namasivayam Ambalavanan and Waldemar A. Carlo

Anoxia is a term used to indicate the consequences of complete lack of oxygen as a result of a number of primary causes. Hypoxemia refers to decreased arterial concentration of oxygen. Hypoxia refers to a decreased oxygenation to cells or organs. Ischemia refers to blood flow to cells or organs that is insufficient to maintain their normal function. Hypoxic–ischemic encephalopathy (HIE) is an important cause of permanent damage to CNS tissues that may result in neonatal death or manifest later as cerebral palsy or developmental delay. Approximately 20-30% of infants with HIE die in the neonatal period, and 33-50% of survivors are left with permanent neurodevelopmental abnormalities (cerebral palsy, mental retardation). The greatest risk of adverse outcome is seen in infants with severe fetal acidosis (pH <7.07) (90% death/impairment) and a base deficit >25 mmol/L (72% mortality). Multigorgan failure and insult can occur (Table 99-2).

ETIOLOGY

Most neonatal encephalopathic or seizure disorders, in the absence of major congenital malformations or syndromes, appear to be caused by perinatal events. Brain MRI or autopsy findings in full-term neonates with encephalopathy demonstrate that 80% have acute injuries, <1% have prenatal injuries, and 3% have non–hypoxic-ischemic diagnoses. Fetal hypoxia may be caused by various disorders in the mother, including (1) inadequate oxygenation of maternal blood from hypoventilation during anesthesia, cyanotic heart disease, respiratory failure, or carbon monoxide poisoning; (2) low maternal blood pressure from acute blood loss, spinal anesthesia, or compression of the vena cava and aorta by the gravid uterus; (3) inadequate relaxation of the uterus to permit placental filling as a result of uterine tetany caused by the administration of excessive oxytocin; (4) premature separation of the placenta; (5) impedance to the circulation of blood through the umbilical cord as a result of compression or knotting of the cord; and (6) placental insufficiency from toxemia or postmaturity.

Placental insufficiency often remains undetected on clinical assessment. Intrauterine growth restriction may develop in chronically hypoxic fetuses without the traditional signs of fetal distress. Doppler umbilical waveform velocimetry (demonstrating increased fetal vascular resistance) and cordocentesis (demonstrating fetal hypoxia and lactic acidosis) identify a chronically hypoxic infant (see Chapter 96). Uterine contractions may further reduce umbilical oxygenation, depressing the fetal cardiovascular system and CNS and resulting in low Apgar scores and respiratory depression at birth.

After birth, hypoxia may be caused by (1) failure of oxygenation as a result of severe forms of cyanotic congenital heart disease or severe pulmonary disease; (2) severe anemia (severe hemorrhage, hemolytic disease); or (3) shock severe enough to interfere with the transport of oxygen to vital organs from overwhelming sepsis, massive blood loss, and intracranial or adrenal hemorrhage.

PATHOPHYSIOLOGY AND PATHOLOGY

The topography of injury typically correlates with areas of decreased cerebral blood flow. After an episode of hypoxia and ischemia, anaerobic metabolism occurs and generates increased amounts of lactate and inorganic phosphates. Excitatory and toxic amino acids, particularly glutamate, accumulate in the damaged tissue. Increased amounts of intracellular sodium and calcium may result in tissue swelling and cerebral edema. There is also increased production of free radicals and nitric oxide in these tissues. The initial circulatory response of the fetus is increased shunting through the ductus venosus, ductus arteriosus, and foramen ovale, with transient maintenance of perfusion of the brain, heart, and adrenals in preference to the lungs, liver, kidneys, and intestine.

The pathology of hypoxia–ischemia depends on the affected organ and the severity of the injury. Early congestion, fluid leak from increased capillary permeability, and endothelial cell swelling may then lead to signs of coagulation necrosis and cell death. Congestion and petechiae are seen in the pericardium, pleura, thymus, heart, adrenals, and meninges. Prolonged intrauterine hypoxia may result in inadequate perfusion of the periventricular white matter, resulting, in turn, in PVL. Pulmonary arteriole smooth muscle hyperplasia may develop, which predisposes the infant to pulmonary hypertension (see Chapter 101.7). If fetal distress produces gasping, the amniotic fluid contents (meconium, squames, lanugo) may be aspirated into the trachea or lungs.

The combination of chronic fetal hypoxia and acute hypoxic-ischemic injury around the time of birth results in gestational age-specific neuropathology (Table 99-3). Term infants demonstrate neuronal necrosis of the cortex (later, cortical atrophy) and parasagittal

---

**Table 99-2 Multigorgan Systemic Effects of Asphyxia**

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>EFFECT(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>HIE, infarction, intracranial hemorrhage, seizures, cerebral edema, hypotonia, hypertension</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Myocardial ischemia, poor contractility, cardiac stunning, tricuspid insufficiency, hypotension</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Pulmonary hypertension, pulmonary hemorrhage, RDS</td>
</tr>
<tr>
<td>Renal</td>
<td>Acute tubular or cortical necrosis</td>
</tr>
<tr>
<td>Adrenal</td>
<td>Adrenal hemorrhage</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Perforation, ulceration with hemorrhage, necrosis</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Inappropriate secretion of antidiuretic hormone, hyponatremia, hypoglycemia, hypocalcemia, myoglobinuria</td>
</tr>
<tr>
<td>Integument</td>
<td>Subcutaneous fat necrosis</td>
</tr>
<tr>
<td>Hematology</td>
<td>Disseminated intravascular coagulation</td>
</tr>
</tbody>
</table>
Bibliography


ischemic injury. Preterm infants demonstrate PVL (later, spastic diplegia), status marmoratus of the basal ganglia, and IVH. Term more often than preterm infants have focal or multifocal cortical infarcts that manifest clinically as focal seizures and hemiplegia.

**CLINICAL MANIFESTATIONS**

Intrauterine growth restriction with increased vascular resistance may be the first indication of fetal hypoxia. During labor, the fetal heart rate slows and beat-to-beat variability declines. Continuous heart rate recording may reveal a variable or late deceleration pattern (see Fig. 96-4). Particularly in infants near term, these signs should lead to the administration of high concentrations of oxygen to the mother and consideration of immediate delivery to avoid fetal death and CNS damage.

At delivery, the presence of meconium-stained amniotic fluid indicates that fetal distress may have occurred. At birth, affected infants may be depressed and may fail to breathe spontaneously. During the ensuing hours, they may remain hypotonic or change from a hypotonic to a hypertonic state, or their tone may appear normal (Tables 99-4 and 99-5). Pallor, cyanosis, apnea, a slow heart rate, and unresponsiveness to stimulation are also signs of HIE. Cerebral edema may develop during the next 24 hr and result in profound brainstem depression. During this time, seizure activity may occur; it may be severe and refractory to the usual doses of anticonvulsants. Though most often a result of the HIE, seizures in asphyxiated newborns may also be a result of hypocalcemia, hypoglycemia, or infection.

In addition to CNS dysfunction, systemic organ dysfunction is noted in up to 80% of affected neonates; heart failure and cardiogenic shock, persistent pulmonary hypertension, RDS, gastrointestinal perforation, and acute kidney injury are associated with perinatal asphyxia secondary to inadequate perfusion (see Table 99-2).

The severity of neonatal encephalopathy depends on the duration and timing of injury. Symptoms develop over a series of days, making it important to perform serial neurologic examinations (see Tables 99-4 and 99-5). During the initial hours after an insult, infants have a depressed level of consciousness. Periodic breathing with apnea or bradycardia is present, but cranial nerve functions are often spared with intact pupillary responses and spontaneous eye movement. Seizures are common with extensive injury. Hypotonia is also common as an early manifestation.

**DIAGNOSIS**

Diffusion-weighted MRI is the preferred imaging modality in neonates with HIE because of its increased sensitivity and specificity early in the process and its ability to outline the topography of the lesion (Figs. 99-5 to 99-8, Table 99-6). CT scans are helpful in identifying focal hemorrhagic lesions, diffuse cortical injury, and damage to the basal ganglia; CT has limited ability to identify cortical injury during the 1st few days of life. Ultrasonography has limited utility in evaluation of hypoxic injury in the term infant; it is the initial preferred modality in evaluation of the preterm infant.

**Table 99-3**

<table>
<thead>
<tr>
<th>AREA OF INJURY</th>
<th>LOCATION OF INJURY</th>
<th>CLINICAL CORRELATE(S)</th>
<th>LONG-TERM SEQUELA(E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective neuronal necrosis</td>
<td>Entire neuraxis, deep cortical area, brainstem and pons/subicular</td>
<td>Stupor or coma, Seizures, Hypotonia, Oculomotor abnormalities, Suck/swallow abnormalities</td>
<td>Cognitive delay, Cerebral palsy, Dystonia, Seizure disorder, Ataxia, Bulbar and pseudobulbar palsy</td>
</tr>
<tr>
<td>Parasagittal injury</td>
<td>Cortex and subcortical white matter, Parasagittal regions, especially posterior</td>
<td>Proximal limb weakness, Upper extremities affected more than lower extremities</td>
<td>Spastic quadriplegia, Cognitive delay, Visual and auditory processing difficulty</td>
</tr>
<tr>
<td>Focal ischemic necrosis</td>
<td>Cortex and subcortical white matter, Vascular injury (usually middle cerebral artery distribution)</td>
<td>Unilateral findings, Seizures common and typically focal</td>
<td>Hemiparesis, Seizures, Cognitive delays</td>
</tr>
<tr>
<td>Periventricular injury</td>
<td>Injury to motor tracts, especially lower extremity</td>
<td>Bilateral and symmetric weakness in lower extremities, More common in preterm infants</td>
<td>Spastic diplegia</td>
</tr>
</tbody>
</table>


**Table 99-4**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>LEVEL OF VARIABLE</th>
<th>ODDS RATIO</th>
<th>SCORE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posture</td>
<td>Normal</td>
<td>0.037</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Distal flexion</td>
<td>0.401</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Decerebrate</td>
<td>1</td>
<td>27</td>
</tr>
<tr>
<td>Spontaneous activity</td>
<td>Normal/decreased</td>
<td>0.147</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Base deficit of first postnatal blood gas analysis</td>
<td>&lt;15 mmol/L</td>
<td>0.073</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>15-22 mmol/L</td>
<td>0.304</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>&gt;22 mmol/L</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Apgar score at 5 min</td>
<td>7-10</td>
<td>0.082</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>4-6</td>
<td>0.676</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>0-3</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Chronic hypertension/ preeclampsia/eclampsia</td>
<td>Yes</td>
<td>0.2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

*The total score is obtained by adding the scores for each of the variables. Interpretation of the total score is as follows: <23: no death or moderate/severe disability even without hypothermia; 23-28: probable benefit from hypothermia; 29-52: possible benefit; >52: death/disability likely despite hypothermia. =172.

The Fetus and the Neonatal Infant

Table 99-5  HIE in Term Infants

<table>
<thead>
<tr>
<th>SIGNS</th>
<th>STAGE 1</th>
<th>STAGE 2</th>
<th>STAGE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of consciousness</td>
<td>Hyperalert</td>
<td>Lethargic</td>
<td>Stuporous, coma</td>
</tr>
<tr>
<td>Muscle tone</td>
<td>Normal</td>
<td>Hypotonic</td>
<td>Flaccid</td>
</tr>
<tr>
<td>Posture</td>
<td>Normal</td>
<td>Flexion</td>
<td>Decerebrate</td>
</tr>
<tr>
<td>Tendon reflexes/clonus</td>
<td>Hyperactive</td>
<td>Hyperactive</td>
<td>Absent</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Moro reflex</td>
<td>Strong</td>
<td>Weak</td>
<td>Absent</td>
</tr>
<tr>
<td>Pupils</td>
<td>Mydriasis</td>
<td>Miosis</td>
<td>Unequal, poor light reflex</td>
</tr>
<tr>
<td>Seizures</td>
<td>None</td>
<td>Common</td>
<td>Decerebration</td>
</tr>
<tr>
<td>Electroencephalographic</td>
<td>Normal</td>
<td>Low voltage changing to seizure activity</td>
<td>Burst suppression to isoelectric</td>
</tr>
<tr>
<td>findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>&lt;24 hr if progresses; otherwise, may remain normal</td>
<td>24 hr-14 days</td>
<td>Days to weeks</td>
</tr>
<tr>
<td>Outcome</td>
<td>Good</td>
<td>Variable</td>
<td>Death, severe deficits</td>
</tr>
</tbody>
</table>


Figure 99-5  MR images of selective neuronal injury. The infant experienced intrapartum asphyxia and had seizures on the 1st postnatal day. MRI was performed on the 5th postnatal day. A, An axial, fluid-attenuated inversion recovery image shows increased signal in the putamen bilaterally (arrows) but no definite abnormality in the cerebral cortex. B, By contrast, a diffusion-weighted image shows striking increased signal intensity (i.e., decreased diffusion) in the frontal cortex (in addition to a more pronounced basal ganglia abnormality). (From Volpe JJ, editor: Neurology of the newborn, ed 5, Philadelphia, 2008, Saunders/Elsevier, p. 420.)

with HIE. Continuous aEEG monitoring detects subclinical seizure activity during the subacute phase.

**TREATMENT**

Whole body (systemic) or selective cerebral therapeutic hypothermia reduces mortality or major neurodevelopmental impairment in term and near-term infants with HIE. Hypothermia decreases the rate of apoptosis and suppresses production of mediators known to be neurotoxic, including extracellular glutamate, free radicals, nitric oxide, and lactate.

Isolated cerebral cooling or more often systemic induced servo controlled hypothermia to a core (rectal) temperature of 33.5°C (92.3°F) within the 1st 6 hr after birth (duration 72 hr) reduces mortality and major neurodevelopmental impairment at 18 mo of age. Systemic hypothermia may result in more uniform cooling of the brain and deeper CNS structures. Infants treated with systemic hypothermia have a lower incidence of cortical neuronal injury on MRI. Complications of induced hypothermia include thrombocytopenia (usually without bleeding), reduced heart rate, and subcutaneous fat necrosis (associated with hypercalcemia in some) and the potential for overcooling and the cold injury syndrome. The latter is avoided with a servocontrolled cooling system. Therapeutic hypothermia may theoretically alter drug metabolism, prolong the QT interval, and effect the interpretation of blood gases. In practice, none of these concerns have been observed during therapeutic hypothermia.

Phenobarbital, the drug of choice for seizures, is given with an intravenous loading dose (20 mg/kg); additional doses of 5-10 mg/kg (up to 40-50 mg/kg total) may be needed. Phenytoin (20 mg/kg
Figure 99-6 MR images of hypoxic-ischemic injury to basal ganglia and thalamus. MRI was performed in a 5 day old infant who experienced severe perinatal asphyxia. A, Note, in this parasagittal T1-weighted image, the markedly increased signal intensity in the basal ganglia, especially the putamen (arrowheads) and the thalamus (arrow). B, An axial proton density image also demonstrates the injury well in the same distribution. (From Volpe JJ, editor: Neurology of the newborn, ed 5, Philadelphia, 2008, Saunders/Elsevier, p. 420.)

Table 99-6 Major Aspects of MRI in the Diagnosis of HIE in the Term Infant

<table>
<thead>
<tr>
<th>Major Conventional MRI Findings in the First Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral cortical gray-white differentiation lost (on T1W or T2W)</td>
</tr>
<tr>
<td>Cerebral cortical high signal (T1W and FLAIR), especially in parasagittal periorlindic cortex</td>
</tr>
<tr>
<td>Basal ganglia–thalamus, high signal (T1W and FLAIR, usually associated with the cerebral cortical changes but possibly alone with increased signal in brainstem tegmentum in cases of acute severe insults</td>
</tr>
<tr>
<td>Parasagittal cerebral cortex, subcortical white matter, high signal (T1W and FLAIR)</td>
</tr>
<tr>
<td>Periventricular white matter, decreased signal (T1W) or increased signal (T2W)</td>
</tr>
<tr>
<td>Posterior limb of internal capsule, decreased signal (T1W or FLAIR)</td>
</tr>
<tr>
<td>Cerebrum in a vascular distribution, decreased signal (T1W), but much better visualized as decreased diffusion (increased signal) on diffusion-weighted MRI</td>
</tr>
</tbody>
</table>

Diffusion-weighted MRI more sensitive than conventional MRI, especially in 1st days after birth, when former shows decreased diffusion (increased signal) in injured areas

FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; T1W and T2W, T1- and T2-weighted images.


Figure 99-7 MR image of a parasagittal cerebral injury. A coronal T1-weighted image, obtained on the 5th postnatal day in an asphyxiated term infant, shows striking triangular lesions in the parasagittal areas bilaterally; increased signal intensity is also apparent in the basal ganglia and thalamus bilaterally. (From Volpe JJ, editor: Neurology of the newborn, ed 5, Philadelphia, 2008, Saunders/Elsevier, p. 421.)
The epilepticus, multifocal seizures and multiple anticonvulsant medications during therapeutic hypothermia, is associated with a poor prognosis. Subclinical (EEG detected) seizures have a better prognosis.

Additional therapy for infants with HIE includes supportive care directed at management of organ system dysfunction. Hyperthermia has been found to be associated with impaired neurodevelopment, so it is important to prevent hyperthermia before initiation of hypothermia. Careful attention to ventilatory status, and adequate ventilation, so it is important to prevent hyperthermia before initiation of hypothermia, is associated with a poor outcome. Microcephaly and poor head growth during the first year of life also correlate with injury to the basal ganglia and white matter and adverse developmental outcome at 12 mo. All survivors of moderate to severe encephalopathy require comprehensive high-risk medical and developmental follow-up. Early identification of neurodevelopmental problems allows prompt referral for developmental, rehabilitative, neurologic care, and early intervention services so that the best possible outcome can be achieved.

**Brain death** after neonatal HIE is diagnosed from the clinical findings of coma unresponsive to pain, auditory, or visual stimulation; apnea with \( P_{C_{O_2}} \) rising from 40 to >60 mm Hg without ventilatory support; and absence of brainstem reflexes (pupillary, oculocephalic, oculovestibular, corneal, gag, sucking) (see Chapter 68.1). These findings must occur in the absence of hypothermia, hypotension, and elevations of depressant drugs (phenobarbital). An absence of cerebral blood flow on radionuclide scans and of electrical activity on EEG (electrocerebral silence) is inconsistently observed in clinically brain-dead neonatal infants. Persistence of the clinical criteria for 2 days in term infants and 3 days in preterm infants predicts brain death in most asphyxiated newborns. Nonetheless, no universal agreement has been reached regarding the definition of neonatal brain death. Consideration of withdrawal of life support should include discussions with the family, the healthcare team, and, if there is disagreement, an ethics committee. The best interest of the infant involves judgments about the benefits and harm of continuing therapy or avoiding ongoing futile therapy.

**Bibliography is available at Expert Consult.**

### 99.6 Spine and Spinal Cord

*Waldemar A. Carlo and Namasiyavam Ambalavanam*

Injury to the spine/spinal cord during birth is rare but can be devastating. Strong traction exerted when the spine is hyperextended or when the direction of pull is lateral, or forceful longitudinal traction on the trunk while the head is still firmly engaged in the pelvis, especially when combined with flexion and torsion of the vertical axis, may produce fracture and separation of the vertebrae. Such injuries are most likely to occur when difficulty is encountered in delivering the shoulders in cephalic presentations and the head in breech presentations. The injury occurs most commonly at the level of the 4th cervical vertebra with cephalic presentations and the lower cervical–upper thoracic vertebrae with breech presentations. Transection of the cord may

![Figure 99-8 MR images of focal ischemic cerebral injury. MRI was performed on the 3rd postnatal day. A, An axial T2-weighted image shows a lesion in the distribution of the main branch of the left middle cerebral artery. B, A diffusion-weighted image demonstrates the lesion more strikingly. (From Volpe JJ, editor: Neurology of the newborn, ed 5, Philadelphia, 2008, Saunders/Elsevier, p. 422.)](image-url)
Bibliography


occur with or without vertebral fractures; hemorrhage and edema may produce neurologic signs that are indistinguishable from those of transection except that they may not be permanent. Areflexia, loss of sensation, and complete paralysis of voluntary motion occur below the level of injury, although the persistence of a withdrawal reflex mediated through spinal centers distal to the area of injury is frequently misinterpreted as representing voluntary motion. If the injury is severe, the infant, who from birth may be in poor condition because of respiratory depression, shock, or hypothermia, may deteriorate rapidly to death within several hours before any neurologic signs are obvious. Alternatively, the course may be protracted, with symptoms and signs appearing at birth or later in the 1st wk; immobility, flaccidity, and associated brachial plexus injuries may not be recognized for several days. Constipation may also be present. Some infants survive for prolonged periods, their initial flaccidity, immobility, and areflexia being replaced after several weeks or months by rigid flexion of the extremities, increased muscle tone, and spasms. Apnea on day 1 and poor motor recovery by 3 mo are poor prognostic signs.

The differential diagnosis of spine/spinal cord injury includes amyotonia congenita and myelodysplasia associated with spina bifida occulta. Ultrasonography or, more often, MRI confirms the diagnosis. Treatment of the survivors is supportive, including home ventilation; patients often remain permanently disabled. When a fracture or dislocation is causing spinal compression, the prognosis is related to the time elapsed before the compression is relieved.

Bibliography is available at Expert Consult.

99.7 Peripheral Nerve Injuries
Waldemar A. Carlo and Namasiyavam Ambalavan

BRACHIAL PALSY
Brachial plexus injury is a common problem, with an incidence of 0.6-4.6/1,000 live births. Injury to the brachial plexus may cause paralysis of the upper part of the arm with or without paralysis of the forearm or hand or, more commonly, paralysis of the entire arm. These injuries occur in macrosomic infants and when lateral traction is exerted on the head and neck during delivery of the shoulder in a vertex presentation, when the arms are extended over the head in a breech presentation, or when excessive traction is placed on the shoulders. Approximately 45% of brachial plexus injuries are associated with shoulder dystocia. In Erb-Duchenne paralysis, the injury is limited to the 5th and 6th cervical nerves. The infant loses the power to abduct the arm from the shoulder, rotate the arm externally; and supinate the forearm. The characteristic position consists of adduction and internal rotation of the arm with pronation of the forearm. Power to extend the forearm is retained, but the biceps reflex is absent; the Moro reflex is absent on the affected side (Fig. 99-9). The outer aspect of the arm may have some sensory impairment. Power in the forearm and hand grasps is preserved unless the lower part of the plexus is also injured; the presence of hand grasp is a favorable prognostic sign. When the injury includes the phrenic nerve, alteration in diaphragmatic excursion may be observed with ultrasonography or fluoroscopy.

Klumpke paralysis is a rare form of brachial palsy, in which injury to the 7th and 8th cervical nerves and the 1st thoracic nerve produces a paralyzed hand and ipsilateral ptosis and miosis (Horner syndrome) if the sympathetic fibers of the 1st thoracic root are also injured. Mild cases may not be detected immediately after birth. Differentiation must be made from cerebral injury; from fracture, dislocation, or epiphysial separation of the humerus; and from fracture of the clavicle. MRI demonstrates nerve root rupture or avulsion.

Full recovery occurs in most patients; prognosis depends on whether the nerve was merely injured or was lacerated. If the paralysis was a result of edema and hemorrhage about the nerve fibers, function should return within a few months; if it was because of laceration, permanent damage may result. Involvement of the deltoid is usually the most serious problem and may result in shoulder drop secondary to muscle atrophy. In general, paralysis of the upper part of the arm has a better prognosis than paralysis of the lower part.

Treatment consists of initial conservative management with monthly follow-up and a decision for surgical intervention by 3 mo if function has not improved. Partial immobilization and appropriate positioning are used to prevent the development of contractures. In upper arm paralysis, the arm should be abducted 90 degrees with external rotation at the shoulder, full supination of the forearm, and slight extension at the wrist with the palm turned toward the face. This position may be achieved with a brace or splint during the 1st 1-2 wk. Immobilization should be intermittent throughout the day while the infant is asleep and between feedings. In lower arm or hand paralysis, the wrist should be splinted in a neutral position, and padding placed in the fist. When the entire arm is paralyzed, the same treatment principles should be followed. Gentle massage and range-of-motion exercises may be started by 7-10 days of age. Infants should be closely monitored with active and passive corrective exercises. If the paralysis persists without improvement for 3 mo, neuroplasty, neurolysis, end-to-end anastomosis, and nerve grafting offer hope for partial recovery.

The type of treatment and the prognosis depend on the mechanism of injury and the number of nerve roots involved. The mildest injury to a peripheral nerve (neuapraxia) is due to edema and heals spontaneously within a few weeks. Axonotmesis is more severe and is a consequence of nerve fiber disruption with an intact myelin sheath; function usually returns in a few months. Total disruption of nerves (neurotmesis) or root avulsion is the most severe, especially if it involves C5-T1; microsurgical repair may be indicated. Fortunately, most (75%) injuries are at the root level C5-C6, involve neuapraxia and axonotmesis, and should heal spontaneously. Botulism toxin may be used to treat biceps-triceps co-contractions.

PHRENIC NERVE PARALYSIS
Phrenic nerve injury (3rd, 4th, 5th cervical nerves) with diaphragmatic paralysis must be considered when cyanosis and irregular and labored respirations develop. Such injuries, usually unilateral, are associated with ipsilateral upper brachial palsy. Because breathing is thoracic in type, the abdomen does not bulge with inspiration. Breath
Bibliography


sounds are diminished on the affected side. The thrust of the dia-
phragm, which may often be felt just under the costal margin on the
normal side, is absent on the affected side. The diagnosis is established
by ultrasonographic or fluoroscopic examination, which reveals eleva-
tion of the diaphragm on the paralyzed side and seesaw movements of
the 2 sides of the diaphragm during respiration.

No specific treatment is available; infants should be placed on the
involved side and given oxygen if necessary. Initially, intravenous feed-
ings may be needed; later, progressive gavage or oral feeding may be
started, depending on the infant's condition. Pulmonary infections are
a serious complication. Recovery usually occurs spontaneously by
1-3 mo; rarely, surgical plication of the diaphragm may be indicated.

**FACIAL NERVE PALSY**

Facial palsy is usually a peripheral paralysis that results from pressure
over the facial nerve in utero, from efforts during labor, or from forceps
use during delivery. Rarely, it may result from nuclear agenesis of the
facial nerve. Peripheral paralysis is flaccid and, when complete, involves
the entire side of the face, including the forehead. When the infant
cries, movement occurs only on the nonparalyzed side of the face, and
the mouth is drawn to that side. On the affected side the forehead is
smooth, the eye cannot be closed, the nasolabial fold is absent, and the
corner of the mouth droops. The forehead wrinkles on the affected side
with central paralysis because only the lower 2/3 of the face is involved.
The infant also usually has other manifestations of intracranial injury,
most commonly 6th nerve palsy. The prognosis depends on whether
the nerve was injured by pressure or the nerve fibers were torn.
Improvement occurs within a few weeks in the former instance. Care
of the exposed eye is essential. Neuroplasty may be indicated when the
paralysis is persistent. Facial palsy may be confused with absence of
the depressor muscles of the mouth, which is a benign problem.

Other peripheral nerves are seldom injured in utero or at birth
except when they are involved in fractures or hemorrhage.

*Bibliography is available at Expert Consult.*
Bibliography
RESPIRATORY DISTRESS AND FAILURE

Disorders of respiration in newborn infants can be categorized as either central nervous system (CNS) failure, representing depression or failure of the respiratory center, or peripheral respiratory difficulty, indicating interference with the alveolar exchange of oxygen and carbon dioxide. Cyanosis occurs in both groups (see Table 98-1). Respiratory problems encountered in the delivery room are most frequently those of airway obstruction and depression of the CNS (maternal medications, asphyxia) with an absence of adequate respiratory effort. Respiratory distress in the presence of good respiratory effort should lead to an immediate consideration of the underlying cause and is an indication for radiographic examination of the chest.

If respiratory movements are made with the mouth closed but the infant fails to move air in and out of the lungs, bilateral choanal atresia (see Chapter 376) or other obstruction of the upper respiratory tract should be suspected. The mouth should be opened, and the mouth and pharynx cleared of secretions with gentle suction. An oropharyngeal airway should be inserted, and the source of the obstruction sought immediately. If effective respiratory flow is not produced by opening the infant's mouth and clearing the airway, laryngoscopy is indicated. With obstructive malformations of the mandible, epiglottis, larynx, or trachea, an endotracheal tube should be inserted; prolonged endotracheal intubation or tracheostomy may be required. Respiratory failure caused by CNS depression or injury may require continuous mechanical ventilation.

Hypoplasia of the mandible (Pierre Robin, Stickler, DiGeorge, and other syndromes; see Chapters 308 and 311) with posterior displacement of the tongue may result in symptoms similar to those of choanal atresia and may be temporarily relieved by pulling the tongue or mandible forward or placing the infant in the prone position. A scaphoid abdomen suggests a diaphragmatic hernia or eventration, as does asymmetry in contour or movement of the chest or a shift of the apical impulse of the heart; these latter manifestations are also compatible with tension pneumothorax. A pneumothorax can be the presenting symptom in infants with pulmonary hypoplasia, renal malformations, or both.

Pulmonary causes of respiratory difficulty are discussed in Chapter 101.

FAILURE TO INITIATE OR SUSTAIN RESPIRATION

Failure to initiate or sustain respiratory effort is common at birth. Infants with primary apnea respond to stimulation by establishing normal breathing. Infants with secondary apnea need ventilatory assistance. Secondary apnea usually originates in the CNS as a result of asphyxia or peripherally because of neuromuscular disorders. Prematurity alone is seldom a causative factor, except in infants weighing <1,500 g. Intrapulmonary problems, such as respiratory distress syndrome, pulmonary hypoplasia associated with oligohydramnios as in Potter syndrome or neuromuscular diseases, bilateral pleural effusions (hydrops fetalis), pneumothorax, and severe intrauterine pneumonia, may at times result in poor ventilation despite strong respiratory efforts. The lungs in affected infants may be noncompliant, and efforts to begin respirations may be inadequate to initiate sufficient ventilation.

Respiratory depression may occur from administration of morphine, meperidine, fentanyl, barbiturates, or tranquilizers to the mother shortly before delivery or from maternal anesthesia given during the 2nd stage of labor. This sequela may be minimized by the use of appropriate analgesic and anesthetic practices. Treatment includes initial physical stimulation and securing of a patent airway. If effective ventilation is not initiated, artificial breathing with a bag and mask must be instituted. At the same time, if the respiratory depression is caused by an opiate, naloxone hydrochloride (Narcan), 0.1 mg/kg, should be given intravenously or intramuscularly. Naloxone is contraindicated in infants born to mothers with opiate addiction as it may precipitate acute neonatal withdrawal with seizures. Inhalation treatments and repeated positive pressure ventilation are continued until the infant is able to sustain ventilation. CNS-stimulant drugs should not be used because they are ineffective and may be harmful. External cardiac massage, correction of acidosis, and circulatory support with drugs may be important adjuncts to ventilation in the severely asphyxiated infant.

NEONATAL RESUSCITATION

Although the majority of babies undergo a smooth physiologic transition and breathe effectively after delivery, 5-10% requires active intervention to establish normal cardiorespiratory function. The goals of neonatal resuscitation are to prevent the morbidity and mortality...
associated with hypoxic–ischemic tissue (brain, heart, kidney) injury and to reestablish adequate spontaneous respiration and cardiac output. High-risk situations should be anticipated from the history of the pregnancy, labor, and delivery and identification of signs of fetal distress. Infants who are born limp, cyanotic, apneic, or pulseless require immediate resuscitation before assignment of the 1-min Apgar score. Rapid and appropriate resuscitative efforts improve the likelihood of preventing brain damage and achieving a successful outcome.

Guidelines for neonatal resuscitation propose an "integrated" assessment/response approach for the initial evaluation of an infant, consisting of simultaneous assessment of infant color, general appearance, and risk factors. The fundamental principles include evaluation of the airway, establishing effective respiration and adequate circulation; the guidelines also highlight the assessment and response to the neonatal heart rate and the management of infants with meconium-stained amniotic fluid.

Immediately after birth, an infant in need of resuscitation should be placed under a radiant heater and dried (to avoid passive hyperthermia), positioned with the head down and slightly extended; the airway should be cleared by suctioning, and gentle tactile stimulation provided (slapping the foot, rubbing the back). Simultaneously, the infant’s color, heart rate, and respiratory effort should be assessed (Fig. 100-1).

The steps in neonatal resuscitation follow the ABCs: A, anticipate and establish a patent airway by suctioning and, if necessary, performing endotracheal intubation; B, initiate breathing by using tactile stimulation or positive-pressure ventilation with a bag-and-mask or through an endotracheal tube; C, maintain the circulation with chest compression and medications, if needed. Figure 100-1 outlines the steps to follow for immediate neonatal evaluation and resuscitation (see also Chapter 67).

If no respirations are noted, or if the heart rate is <100 beats/min, positive-pressure ventilation is given through a tightly fitted face-bag-and-mask for 15-30 sec. In infants with severe respiratory depression that does not respond to positive-pressure ventilation via bag-and-mask, endotracheal intubation should be performed. Many authorities recommend early intubation for extremely low birthweight preterm infants. Table 100-1 lists guidelines for endotracheal tube size and depth of insertion in infants with different birthweights. If the heart rate does not improve after 30 sec with bag-and-mask (or endotracheal) ventilation and remains below 100 beats/min, ventilation is continued and chest compression should be initiated over the lower third of the sternum at a rate of 90 compressions/min. The ratio of compressions to ventilation is 3:1 (90 compressions:30 breaths). If the heart rate remains <60 beats/min despite effective compressions and ventilation, administration of epinephrine should be considered. Persistent bradycardia in neonates is usually attributable to hypoxia resulting from respiratory arrest and often responds rapidly to effective ventilation alone. Persistent bradycardia despite what appears to be adequate resuscitation suggests inadequate ventilation or more severe cardiac compromise. Poor response to ventilation may be a result of a loosely fitted mask, poor positioning of the endotracheal tube, intrasophageal intubation, airway obstruction, insufficient pressure, pleural effusions, pneumothorax, excessive air in the stomach, asystole, hypovolemia, diaphragmatic hernia, or prolonged intravascular asphyxia.

In the past, the inspired gas for neonatal resuscitation had been 100% oxygen. Resuscitation with room air in term infants is equally effective and may reduce the risk of hyperoxia, which is associated with decreased cerebral blood flow and generation of oxygen free radicals. Room air is the preferred initial gas for neonatal resuscitation in term infants; if the neonate does not achieve normal oxygen saturation levels within 90 sec, increasing concentrations of oxygen should be blended in (up to 100% oxygen) until normal oxygen saturation levels are achieved. If pulmonary hypertension is suspected (meconium aspiration, diaphragmatic hernia) one may consider 100% oxygen as the initial gas for resuscitation. Particular attention is required during the resuscitation of very-low birthweight neonates, to monitor oxygen saturation and adjust oxygen concentration using an oxygen blender so as to minimize the risk of hyperoxia and hypoxia.

Although the first breath normally requires pressures as low as 15-20 cm H₂O, pressures as high as 30–40 cm H₂O may be needed. Subsequent breaths are given at a rate of 40–60/min with a pressure of 15-20 cm H₂O. Noncompliant stiff lungs secondary to respiratory distress syndrome, congenital pneumonia, pulmonary hypoplasia, or meconium aspiration may require higher pressures. Successful ventilation is signified by adequate chest rise, symmetric breath sounds, improved pink color, heart rate >100 beats/min, spontaneous respirations, presence of end-tidal CO₂, and improved tone. Various devices to detect exhaled CO₂ and to confirm accurate placement of an endotracheal tube are available commercially. A laryngeal mask airway may be an effective tool to establish an airway, especially if bag and mask ventilation is ineffective or intubation is unsuccessful.
If the infant has respiratory depression and the mother has received an analgesic narcotic drug within 4 hr prior to delivery, naloxone hydrochloride (0.1 mg/kg) is given while adequate ventilation is maintained. Breathing in the depressed infant should be maintained until a response to naloxone is noted. Continuous observation of the infant is important because repeated doses of naloxone may be needed even after the infant has been transferred to the nursery owing to the short half-life of naloxone.

Medications are rarely required but should be administered when the heart rate is <60 beats/min after 30 sec of combined ventilation and chest compressions or during asystole. The umbilical vein can generally be readily cannulated and used for immediate administration of medications during neonatal resuscitation (Fig. 100-2). The endotracheal tube may be used for the administration of epinephrine if intravenous access is not available and/or for naloxone. Epinephrine (0.1-0.3 mL/kg of a 1:10,000 solution, given intravenously or intratracheally) is given for asystole or for failure to respond to 30 sec of combined resuscitation. The dose may be repeated every 3-5 min. Data in neonates are insufficient to recommend higher doses in infants who are unresponsive to the standard dose. Emergency volume expansion is accomplished with 10-20 mL/kg of an isotonic crystalloid solution or type O Rh-negative red blood cells (in acute hemorrhage). Volume infusions should be used cautiously during the resuscitation of a very-low birth-weight infant. Sodium bicarbonate (2 mEq/kg, 0.5 mEq/mL of a 4.2% solution) is sometimes given and should be administered slowly (1 mEq/kg/min) if metabolic acidosis has been documented and the resuscitation is prolonged. Sodium bicarbonate should be given only after effective ventilation has been established, because such therapy may increase the blood CO2 concentration and produce respiratory acidosis, complicating an existing metabolic acidosis. Restoration of oxygenation and tissue perfusion is the main treatment of metabolic acidosis associated with asphyxia.

Severe asphyxia may also depress myocardial function and cause cardiogenic shock despite the recovery of heart and respiratory rates. Dopamine or dobutamine administered as a continuous infusion (5-20 µg/kg/min) and fluids should be started after the initial resuscitation effort, to improve cardiac output in an infant with poor peripheral perfusion, weak pulses, hypotension, tachycardia, and poor urine output. Epinephrine (0.1-1.0 µg/kg/min) may be indicated for infants in severe shock that does not respond to dopamine or dobutamine (see Chapter 67).

Less-severe degrees of poor cardiopulmonary transition in the delivery room can usually be managed by brief periods of bag-and-mask ventilation. Chest compression and medications are not needed for most neonates who have mild to moderate birth depression. Regardless of the severity of asphyxia or the response to resuscitation, asphyxiated infants should be monitored closely for signs of multiorgan hypoxic-ischemic tissue injury (see Table 99-1 in Chapter 99).

**Table 100-1 Guidelines for Tracheal Tube Size and Depth of Insertion**

<table>
<thead>
<tr>
<th>TUBE SIZE (MM INTERNAL DIAMETER)</th>
<th>DEPTH OF INSERTION FROM UPPER LIP (cm)</th>
<th>WEIGHT (g)</th>
<th>GESTATION (wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>6.5-7</td>
<td>&lt;1,000</td>
<td>&lt;28</td>
</tr>
<tr>
<td>3</td>
<td>7-8</td>
<td>1,000-2,000</td>
<td>28-34</td>
</tr>
<tr>
<td>3/3.5</td>
<td>8-9</td>
<td>2,000-3,000</td>
<td>34-38</td>
</tr>
<tr>
<td>3.5/4.0</td>
<td>≥9</td>
<td>&gt;3,000</td>
<td>&gt;38</td>
</tr>
</tbody>
</table>


**MECONIUM**

Meconium staining of the amniotic fluid may be an indication of fetal stress; therefore, personnel skilled at endotracheal intubation and resuscitation should be present at the delivery. Previously the decision to intubate a neonate was based on the presence and thickness/consistency of the meconium-stained fluid; current evidence no longer supports this practice. If the infant is vigorous with good respiratory effort and a heart rate >100 beats/min, tracheal intubation to aspirate meconium **should not be attempted**; the mouth and nose may be suctioned with a bulb or suction catheter. If the infant is depressed with poor muscle tone and/or a heart rate <100 beats/min, tracheal intubation and suctioning should be performed. The endotracheal tube should be attached to a suction device, and free-flow oxygen should be provided throughout the procedure.

**SHOCK**

Circulatory insufficiency may be present at birth as a result of severe asphyxia or hemorrhage during gestation, labor, or delivery. Causes of blood loss include hemolysis; placental abruption or tear, placenta previa; traumatic injury to the umbilical cord or internal organs; and intracranial bleeding. Clinical manifestations include signs of respiratory distress, cyanosis, pallor, flaccidity, cold mottled skin, tachycardia or bradycardia, hepatosplenomegaly, and, rarely, convulsions. Edema and hepatosplenomegaly suggest hydrops fetalis or heart failure without shock. Shock from overwhelming infection may be present immediately after birth.

Supportive treatment with type O Rh-negative blood or normal saline is indicated for hemorrhage or hypovolemia, respectively. Oxygen should be administered and the metabolic acidosis corrected with sodium bicarbonate. A sympathomimetic agent such as dopamine or dobutamine may be needed to support cardiac output and blood pressure. The diagnosis and treatment of erythroblastosis fetalis are discussed in Chapter 103.2. If infection is present, appropriate antibiotics must be started as soon as possible.

After supportive measures have stabilized the infant’s condition, a specific diagnosis should be established, and appropriate continuing treatment instituted.

**PNEUMOTHORAX**

Infants may experience pneumothorax in the delivery room, resulting in respiratory distress and hypoxia. Approximately 1-2% of infants have pneumothorax after birth; only 0.05-0.07% have symptoms (see Chapter 101.12). The risk is higher in infants requiring positive pressure ventilation or those with meconium-stained amniotic fluid. Rarely, an infant has a congenital malformation that results in lung hypoplasia, such as congenital diaphragmatic hernia or renal agenesis. Clinically, the infant demonstrates respiratory distress and has diminished breath sounds on the affected side. Transillumination may be helpful to confirm the diagnosis, particularly in the low birthweight infant. Emergency evacuation of a pneumothorax without...
radiographic confirmation is indicated in an infant who is unresponsive to resuscitation efforts, and has asymmetric breath sounds, bradycardia, and cyanosis. A 23-gauge butterfly needle or angiocatheter attached to a stopcock and syringe should be inserted perpendicular to the chest wall above the rib in the 4th intercostal space at the level of the nipple (Fig. 100-3). The air is evacuated. The catheter is then inserted with constant negative pressure, and the air evacuated.

**AIRWAY OBSTRUCTION**

Critical fetal and then neonatal airway obstruction represents an emergency in the delivery room. The *ex utero intrapartum treatment* (EXIT) procedure allows time to secure the airway in an infant known to have airway obstruction for a variety of causes, including laryngeal atresia or stenosis, teratomas, hygromas, and oral tumors, before the infant is separated from the placenta. Uteroplacental gas exchange is maintained throughout the procedure. High-risk perinatal care has led to more frequent prenatal diagnosis of many disorders known to cause the *critical high airway obstruction syndrome* (CHAOS) (Fig. 100-4).

**ABDOMINAL WALL DEFECTS**

Appropriate management of patients with abdominal wall defects (omphalocele, gastroschisis) in the delivery room prevents excessive fluid loss and minimizes the risk for injury to the exposed viscera.

![Figure 100-3 Decompression of a pneumothorax.](From Kattwinkel J, Bloom RS, editors: Neonatal resuscitation textbook, ed 5, Elk Grove, IL, 2006, American Academy of Pediatrics, American Heart Association.)

Gastroschisis is the more common defect and typically the intestines are not covered by a membrane. The exposed intestines should be gently placed in a sterile clear plastic bag after delivery. A membrane often covers an omphalocele, and care should be taken to prevent its rupture. The infant should be transferred to a tertiary referral center for surgical consultation and evaluation for other associated anomalies (see Chapter 105).

**INJURY DURING DELIVERY**

**Central Nervous System**

See Chapter 99.

**Viscera**

The liver is the only internal organ other than the brain that is injured with any frequency during the delivery process. Damage usually results from pressure on the liver during delivery of the head in breech presentations. Large infant size, intrauterine asphyxia, coagulation disorders, extreme prematurity, and hepatomegaly are contributing factors. Incorrect cardiac massage is a less-frequent cause. Hepatic rupture may result in the formation of a *subcapsular hematoma*, but the capsule may tamponade further bleeding. Affected infants may appear normal for the 1st 1-3 days. Nonspecific signs related to loss of blood into the hematoma may appear early and include poor feeding, listlessness, pallor, jaundice, tachypnea, and tachycardia. A mass may be palpable in the right upper quadrant, and the abdomen or inguinal area may appear blue. The hematoma may be large enough to cause anemia. Shock and death may occur if the hematoma ruptures into the peritoneal cavity, where the reduced pressure may allow fresh hemorrhage. Early suspicion, ultrasonographic diagnosis, and prompt supportive therapy can decrease the mortality associated with this disorder. Surgical repair of a laceration may be required. Rupture of the spleen may occur alone or in connection with rupture of the liver. The causes, complications, treatment, and prevention are similar.

Although *adrenal hemorrhage* occurs with some frequency, especially after breech delivery, in infants who are large for gestational age or have diabetic mothers, its cause is often undetermined; it may be due to trauma, anoxia, or severe stress, as in overwhelming infection. Ninety percent of adrenal hemorrhages are unilateral; 75% are right-sided. Calcified central hematomas of the adrenal, identified on radiographs or at autopsy in older infants and children, suggest that not all adrenal hemorrhages are immediately fatal. In severe cases, the diagnosis is usually made at postmortem examination. The symptoms are profound shock and cyanosis. A mass may be present in the flank along with overlying skin discoloration; jaundice may also develop. If adrenal hemorrhage is suspected, abdominal ultrasonography may be helpful, and treatment of acute adrenal failure may be indicated (see Chapter 569).

![Figure 100-4 EXIT procedure. Baby with teratoma and critical high airway obstruction syndrome (CHAOS). Trachea is displaced to the lateral neck.](Courtesy of Dr. Mark Wulkan, Pediatric Surgery, Emory University.)
**Fractures**

**Clavicle**
The clavicle is fractured during labor and delivery more frequently than any other bone; it is particularly vulnerable with difficult delivery of the shoulder in vertex presentations and the extended arms in breech deliveries. The infant characteristically does not move the arm freely on the affected side; crepitus and bony irregularity may be palpated, and discoloration is occasionally visible over the fracture site. The Moro reflex is absent on the affected side, and spasm of the sternocleidomastoid muscle with obliteration of the supraclavicular depression at the site of the fracture can be noted. Infants with greenstick clavicle fractures may not have any limitation of movement, and the Moro reflex may be present. The prognosis for this fracture is excellent. **Treatment**, if any, consists of immobilization of the arm and shoulder on the affected side. A remarkable degree of palpable callus develops at the site within a week and may be the initial evidence of the fracture. Fracture of the humerus or brachial palsy may also be responsible for limitation of movement of an arm and absence of a Moro reflex on the affected side.

**Extremities**
In fractures of the long bones, spontaneous movement of the extremity is usually absent (**pseudoparalysis**). The Moro reflex is often absent from the involved extremity. Associated nerve involvement may occur. Satisfactory results of treatment of a fractured humerus are obtained with 2-4 wk of immobilization, during which the arm is strapped to the chest, a triangular splint and a Velpeau bandage are applied, or a cast is applied. For fracture of the femur, good results are achieved with traction-suspension of both lower extremities, even if the fracture is unilateral; the legs are immobilized in a spica cast. Splints are effective for treatment of fractures of the forearm or leg. Healing is usually accompanied by excess callus formation. The prognosis is excellent for fractures of the extremities. Fractures in very-low birthweight infants may be related to osteopenia of prematurity (see Chapter 106).

Dislocations and epiphyseal separations rarely result from birth trauma. The upper femoral epiphysis may be separated by forcible manipulation of the infant’s leg as, for example, in breech extraction or after version. The affected leg shows swelling, slight shortening, limitation of active motion, painful passive motion, and external rotation. The diagnosis is established radiographically. The prognosis is good for milder injuries, but coxa vara frequently results from extensive displacement.

**Nose**
The most prevalent injury to the nose is dislocation of the cartilaginous portion of the septum from the vomerine groove and the columella. The affected infant may have difficulty nursing and some impairment of nasal respiration. On physical examination, the nares appear asymmetric and the nose is flattened. An oral airway is rarely needed, and surgical consultation should be obtained for definitive treatment.

*Bibliography is available at Expert Consult.*
Bibliography


Respiratory disorders are the most frequent cause of admission for neonatal intensive care in both term and preterm infants. Signs and symptoms of respiratory distress include cyanosis, grunting, nasal flaring, retractions, tachypnea, decreased breath sounds with or without rales and/or rhonchi, and pallor. A wide variety of pathologic lesions may be responsible for respiratory disturbances, including pulmonary, airway, cardiovascular, central nervous, infection, and other disorders (Fig. 101-1).

### Figure 101-1 Neonate with acute respiratory distress

<table>
<thead>
<tr>
<th>Abnormal lungs by chest radiograph</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormalities in</td>
</tr>
<tr>
<td>Common Respiratory distress syndromes Transient tachypnea Pneumonia aspiration syndromes Pneumothorax and air leaks Pulmonary edema Pleural effusion Pulmonary hemorrhage</td>
</tr>
<tr>
<td>Uncommon Diaphragmatic hernia Tracheoesophageal fistula Cysts and tumors Congenital lobar emphysema Pulmonary hypoplasia Accessory or sequestered lobes Pulmonary lymphangiecstasia Pulmonary arteriovenous fistula</td>
</tr>
</tbody>
</table>

### Perfusion

<table>
<thead>
<tr>
<th>BP</th>
<th>HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormalities in</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
</tr>
<tr>
<td>Polycythemia</td>
<td></td>
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<tr>
<td>Hypotension</td>
<td></td>
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<tr>
<td>Hypovolemia</td>
<td></td>
</tr>
</tbody>
</table>

### Neuro-muscular findings

- Asphyxia
- Intracranial hemorrhage
- Neuromuscular disorders
- Drugs

### Diaphragm or chest wall

- Chest wall disorders
- Diaphragmatic disorders

### Airway findings

- Upper airway
- Laryngeal
- Lower airway

### CVS findings or echo

- Persistent fetal circulation
- Cyanotic congenital heart disease
- Congestive heart failure

### Abdominal findings

- Ascites
- Necrotizing enterocolitis
- Abdominal mass
- Omphalocele
- Gastrochisis

### Other or mixed findings

- Sepsis
- Acidosis
- Hypothermia
- Hyperthermia
- Hypoglycemia
- Methemoglobinemia

(From Battista MA, Carlo WA: Differential diagnosis of acute respiratory distress in the neonate. In Frantz ID, editor. Tufts University of School of Medicine and Floating Hospital for Children reports on neonatal respiratory diseases, vol 2, issue 3, Newtown, PA, 1992, Associates in Medical Marketing Co.)
It is occasionally difficult to distinguish respiratory from nonrespiratory etiologies on the basis of clinical signs alone. Signs of respiratory distress are an indication for a physical examination and diagnostic evaluation, including a blood gas or pulse oximetry determination and chest x-ray. Timely and appropriate therapy is essential to improve outcome.

**101.1 Transition to Pulmonary Respiration**

Waldemar A. Carlo

Successful establishment of adequate lung function at birth depends on airway patency, functional lung development, and maturity of respiratory control. Fetal lung fluid must be removed and replaced with gas. This process begins before birth as active sodium transport across the pulmonary epithelium drives liquid from the lung lumen into the interstitium with subsequent absorption into the vasculature. Increased levels of circulating catecholamines, vasopressin, prolactin, and glucocorticoids enhance lung fluid adsorption and trigger the change in lung epithelia from a chloride-secretory to a sodium-reabsorptive mode. Functional residual capacity (FRC) must be established and maintained in order to develop a ventilation-perfusion relationship that will provide optimal exchange of oxygen and carbon dioxide between alveoli and blood (see Chapter 421).

**THE FIRST BREATH**

During vaginal delivery, intermittent compression of the thorax facilitates removal of lung fluid. Surfactant lining the alveoli enhances the aeration of gas-free lungs by reducing surface tension, thereby lowering the pressure required to open alveoli. Although spontaneously breathing infants do not need to generate an opening pressure to create airflow, infants requiring positive-pressure ventilation at birth need an opening pressure of 13-32 cm H₂O and are more likely to establish FRC if they generate a spontaneous, negative pressure breath. Expiratory esophageal pressures associated with the first few spontaneous breaths in term newborns range from 45-90 cm H₂O. This high pressure, due to expiration against a partially closed glottis, may aid in the establishment of FRC but would be difficult to mimic safely with use of artificial ventilation. The higher pressures needed to initiate respiration are required to overcome the opposing forces of surface tension (particularly in small airways) and the viscosity of liquid remaining in the airways, as well as to introduce about 50 mL/kg of which remains after the first breath to establish FRC if they generate a spontaneous, negative pressure breath. Expiratory esophageal pressures associated with the first few spontaneous breaths in term newborns range from 45-90 cm H₂O. This high pressure, due to expiration against a partially closed glottis, may aid in the establishment of FRC but would be difficult to mimic safely with use of artificial ventilation. The higher pressures needed to initiate respiration are required to overcome the opposing forces of surface tension (particularly in small airways) and the viscosity of liquid remaining in the airways, as well as to introduce about 50 mL/kg of which remains after the first breath to establish FRC. Air entry into the lungs displaces fluid, decreases hydrostatic pressure in the pulmonary vasculature, and increases pulmonary blood flow. The greater blood flow, in turn, increases the blood volume of the lung and the effective vascular surface area available for fluid uptake. The remaining fluid is removed via the pulmonary lymphatics, upper lung and the effective vascular surface area available for fluid uptake. The process begins before birth as active sodium transport across the pulmonary epithelium drives liquid from the lung lumen into the interstitium with subsequent absorption into the vasculature. Increased levels of circulating catecholamines, vasopressin, prolactin, and glucocorticoids enhance lung fluid adsorption and trigger the change in lung epithelia from a chloride-secretory to a sodium-reabsorptive mode. Functional residual capacity (FRC) must be established and maintained in order to develop a ventilation-perfusion relationship that will provide optimal exchange of oxygen and carbon dioxide between alveoli and blood.

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**101.2 Apnea**

Waldemar A. Carlo

Apnea is a common problem in preterm infants that may be the result of prematurity or an associated illness. In term infants, apnea is always worrisome and demands prompt diagnostic evaluation. Periodic breathing must be distinguished from prolonged apneic pauses, because the latter may be associated with serious illnesses. Apnea is a feature of many primary diseases that affect neonates (Table 101-1). These disorders produce apnea by direct depression of the central nervous system’s control of respiration (hypoglycemia, meningitis, drugs, hemorrhage, seizures), disturbances in oxygen delivery (shock, sepsis, anemia), or ventilation defects (obstruction of the airway, pneumonia, muscle weakness).

**Idiopathic apnea of prematurity** occurs in the absence of identifiable predisposing diseases. Apnea is a disorder of respiratory control and may be obstructive, central, or mixed. **Obstructive apnea** (pharyngeal instability, neck flexion) is characterized by absence of airflow but persistent chest wall motion. Pharyngeal collapse may follow the negative airway pressures generated during inspiration or it may result from incoordination of the tongue and other upper airway muscles.

**Table 101-1: Potential Causes of Neonatal Apnea and Bradycardia**

<table>
<thead>
<tr>
<th>Tract</th>
<th>Potential Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td>Intraventricular hemorrhage, drugs, seizures, hypoxic injury, herniation, neuromuscular disorders, Leigh syndrome, brainstem infarction or anomalies (e.g., olivopontocerebellar atrophy), spinal cord injury after general anesthesia</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Pneumonia, obstructive airway lesions, upper airway collapse, atelectasis, extreme prematurity, laryngeal reflex, phrenic nerve paralysis, pneumothorax, hypoxia</td>
</tr>
<tr>
<td>Infectious</td>
<td>Sepsis, meningitis (bacterial, fungal, viral), respiratory syncytial virus, pertussis</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Oral feeding, bowel movement, necrotizing enterocolitis, intestinal perforation</td>
</tr>
<tr>
<td>Metabolic</td>
<td>↓ Glucose, ↓ calcium, ↑ sodium, ↑ ammonia, ↑ organic acids, ↑ ambient temperature, hypothermia</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Hypotension, hypertension, heart failure, anemia, hypovolemia, vagal tone</td>
</tr>
<tr>
<td>Other</td>
<td>Immaturity of respiratory center, sleep state</td>
</tr>
</tbody>
</table>

**BREATHING PATTERNS IN NEWBORNS**

During sleep in the 1st few mo after birth, normal full-term infants may have episodes when regular breathing is interrupted by short pauses. This periodic breathing pattern, which shifts from a regular rhythmicity to cyclic brief episodes of intermittent apnea, is more common in preterm infants, who may have apneic pauses of 5-10 sec followed by a burst of rapid respirations at a rate of 50-60 breaths/min for 10-15 sec. They rarely have an associated change in color or heart rate, and periodic breathing often stops without apparent reason. Periodic breathing, a normal characteristic of neonatal respiration, has no prognostic significance.
involved in maintaining airway patency. In *central apnea*, which is caused by decreased central nervous system (CNS) stimuli to respiratory muscles, both airflow and chest wall motion are absent. Gestational age is the most important determinant of respiratory control, with the frequency of apnea being inversely related to gestational age. The immaturity of the brainstem respiratory centers is manifested by an attenuated response to carbon dioxide and a paradoxical response to hypoxia that results in apnea rather than the hyperventilation observed after the 1st few mo of life. The most common pattern of idiopathic apnea in preterm neonates is *mixed apnea* (50-75% of cases), with obstructive apnea preceding (usually) or following central apnea. Short episodes of apnea are usually central, whereas prolonged ones are often mixed. Apnea depends on the sleep state; its frequency increases during active (rapid eye movement) sleep.

**CLINICAL MANIFESTATIONS**

The incidence of idiopathic apnea of prematurity varies inversely with gestational age. The onset of idiopathic apnea can be during the 1st 1-2 wk after birth but is often delayed if there is RDS or other causes of respiratory distress. Apneic episodes have been noted to be as frequent on day 1 as throughout the 1st wk in premature infants without respiratory disease. In preterm infants, *serious apnea* is defined as cessation of breathing for longer than 20 sec or for any duration if accompanied by cyanosis and bradycardia. The incidence of associated bradycardia increases with the length of the preceding apnea and correlates with the severity of hypoxia. Short apnea episodes (10 sec) are rarely associated with bradycardia, whereas longer episodes (>20 sec) have a higher incidence of bradycardia. Bradycardia follows the apnea by 1-2 sec in more than 95% of cases and is most often sinus, but on occasion it can be nodal. Vagal responses and, rarely, heart block are causes of bradycardia without apnea. Short oxygen desaturation episodes noted with oxygen saturation monitoring are normal in neonates, and treatment is not necessary.

**TREATMENT**

Infants at risk for apnea should get cardiorespiratory monitoring. Gentle tactile stimulation is often adequate therapy for mild and intermittent episodes. The onset of apnea in a previously well preterm neonate after the 2nd wk of life or in a term infant at any time is a critical event that warrants prompt investigation. Recurrent apnea of prematurity may be treated with caffeine or theophylline. Methylxanthenes increase central respiratory drive by lowering the threshold of response to hypercapnia as well as enhancing contractility of the diaphragm and preventing diaphragmatic fatigue. Caffeine and theophylline are as effective, but caffeine has fewer side effects (less tachycardia and feeding intolerance). Loading doses of 5-7 mg/kg of theophylline (orally) or aminophylline (intravenously) should be followed by doses of 1-2 mg/kg given every 6-12 hr by the oral or intravenous route. Loading doses of 20 mg/kg of caffeine citrate are followed 24 hr later by maintenance doses of 5 mg/kg/24 hr qd, either orally or intravenously. These doses should be monitored through observation of vital signs and clinical response. Serum drug determinations (therapeutic levels: theophylline, 6-10 µg/mL; caffeine, 8-20 µg/mL) are optional because important side effects of these medications are rare. Higher doses of methylxanthenes may be more effective, do not necessarily result in more frequent side effects, and may reduce major neurodevelopmental disabilities. Withholding respiratory stimulants in infants with RDS may result in ventilator dependency, increased bronchopulmonary dysplasia (BPD), and death. Doxapram, known to be a potent respiratory stimulant, acts predominantly on peripheral chemoreceptors and is effective in neonates with apnea of prematurity that is unresponsive to methylxanthenes. Transfusion of packed red blood cells to reduce the incidence of idiopathic apnea is reserved for severely anemic infants. Gastroesophageal reflux is common in neonates, but data do not support a causal relationship between gastroesophageal reflux and apneic events or the use of anti-reflux medications to reduce the frequency of apnea in preterm infants.

**101.3 Respiratory Distress Syndrome (Hyaline Membrane Disease)**

**Waldemar A. Carlo and Ramasivayam Ambalavanan**

**INCIDENCE**

Respiratory distress syndrome occurs primarily in premature infants; its incidence is inversely related to gestational age and birthweight. It occurs in 60-80% of infants <28 wk of gestational age, in 15-30% of those between 32 and 36 wk of gestational age, and rarely in those >37 wk of gestational age. The risk for development of RDS increases with maternal diabetes, multiple births, cesarean delivery, precipitous delivery, asphyxia, cold stress, and a maternal history of previously affected infants. The incidence is highest in preterm male or white infants. The risk of RDS is reduced in pregnancies with chronic or pregnancy-associated hypertension, maternal heroin use, prolonged rupture of membranes, and antenatal corticosteroid prophylaxis.

**ETIOLOGY AND PATHOPHYSIOLOGY**

Surfactant deficiency (decreased production and secretion) is the primary cause of RDS. The failure to attain an adequate FRC and the tendency of affected lungs to become atelectatic correlate with high surface tension and the absence of pulmonary surfactant. The major constituents of surfactant are dipalmitoyl phosphatidylcholine (lecithin), phosphatidylglycerol, apoproteins (surfactant proteins SP-A, SP-B, SP-C, and SP-D), and cholesterol (Fig. 101-2). With advancing gestational age, increasing amounts of phospholipids are synthesized and stored in type II alveolar cells (Fig. 101-3). These surface-active agents are released into the alveoli, where they reduce surface tension and help maintain alveolar stability by preventing the collapse of small air spaces at end-expiration. Because of immaturity, the amounts produced or released may be insufficient to meet postnatal demands. Surfactant is present in high concentrations in fetal lung homogenates by 20 wk of gestation, but it does not reach the surface of the lungs until later. It appears in amniotic fluid between 28 and 32 wk of gestation. Mature levels of pulmonary surfactant are present usually after 35 wk of gestation.
Bibliography
Although rare, genetic disorders may contribute to respiratory distress. Abnormalities in surfactant protein B and C genes as well as a gene responsible for transporting surfactant across membranes (ABCA3) are associated with severe and often lethal familial respiratory disease. Other familial causes of neonatal respiratory distress (not RDS) include alveolar capillary dysplasia, acinar dysplasia, pulmonary lymphangiectasia, and mucopolysaccharidosis.

Synthesis of surfactant depends in part on normal pH, temperature, and perfusion. Asphyxia, hypoxemia, and pulmonary ischemia, particularly in association with hypovolemia, hypotension, and cold stress, may suppress surfactant synthesis. The epithelial lining of the lungs may also be injured by high oxygen concentrations and the effects of respirator management, thereby resulting in a further reduction in surfactant.

Alveolar atelectasis, hyaline membrane formation, and interstitial edema make the lungs less compliant in RDS, so greater pressure is required to expand the alveoli and small airways. The chest wall of the preterm infant, which is highly compliant, offers less resistance than that of the mature infant to the natural tendency of the lungs to collapse. Thus, at end-expiration, the volume of the thorax and lungs tends to approach residual volume, and atelectasis may develop.

Deficient synthesis or release of surfactant, together with small respiratory units and a compliant chest wall, produces atelectasis and results in perfused but not ventilated alveoli, causing hypoxia. Decreased lung compliance, small tidal volumes, increased physiologic dead space, and insufficient alveolar ventilation eventually result in hypercapnia. The combination of hypercapnia, hypoxia, and acidosis produces pulmonary arterial vasoconstriction with increased right-to-left shunting through the foramen ovale and ductus arteriosus and within the lung itself. Progressive injury to epithelial and endothelial cells from atelectasis (atelectrauma), volutrauma, ischemic injury, and oxygen toxicity results in effusion of proteinaceous material into the alveolar spaces (Fig. 101-4).

**CLINICAL MANIFESTATIONS**

Signs of RDS usually appear within minutes of birth, although they may not be recognized for several hours in larger premature infants until rapid, shallow respirations become more obvious. A later onset of tachypnea should suggest other conditions. Some patients require resuscitation at birth because of intrapartum asphyxia or initial severe respiratory distress (especially with a birthweight <1,000 g). Characteristically, tachypnea, prominent (often audible) grunting, intercostal and subcostal retractions, nasal flaring, and cyanosis are noted. Breath sounds may be normal or diminished with a harsh tubular quality, and on deep inspiration, fine crackles may be heard. The natural course of untreated RDS is characterized by progressive worsening of cyanosis and dyspnea. If the condition is inadequately treated, blood pressure may fall; cyanosis and pallor increase, and grunting decreases or disappears, as the condition worsens. Apnea and irregular respirations are ominous signs requiring immediate intervention. Untreated patients may also have a mixed respiratory-metabolic acidosis, edema, ileus, and oliguria. Respiratory failure may occur in infants with rapid progression of the disease. In most cases, the signs reach a peak within 3 days, after which improvement is gradual. Improvement is often heralded by spontaneous diuresis and improved blood gas values at lower inspired oxygen levels and/or lower ventilator support. Death can result from severe impairment of gas exchange, alveolar air leaks (interstitial emphysema, pneumothorax), pulmonary hemorrhage, or IVH. BPD is a form of chronic lung disease that often develops in infants with severe RDS.

**DIAGNOSIS**
The clinical course, chest x-ray findings, and blood gas and acid–base values help establish the clinical diagnosis. On x-ray, the lungs may have a characteristic but not pathognomonic appearance that includes

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**Figure 101-2** Composition of surfactant recovered by alveolar wash. The quantities of the different components are similar for surfactant from the mature lungs of mammals. SP, surfactant protein. (From Jobe AH: Fetal lung development, tests for maturation, induction of maturation, and treatment. In Creasy RK, Resnick R, editors: Maternal-fetal medicine: principles and practice, ed 3, Philadelphia, 1994, WB Saunders.)

**Figure 101-3** A, Fetal rat lung (low magnification), day 20 (term: day 22) showing developing type II cells, stored glycogen (pale areas), secreted lamellar bodies, and tubular myelin. B, Possible pathway for transport, secretion, and reuptake of surfactant. ER, endoplasmic reticulum; GZ, Golgi zone; LMF, lattice (tubular) myelin figure; MLB, mature lamellar body; MVB, multivesicular body; N, nucleus; SLB, small lamellar body. (A courtesy of Mary Williams, MD, University of California, San Francisco; B from Hansen T, Corbet A: Lung development and function. In Taeusch HW, Ballard RA, Avery MA, editors: Schaffer and Avery’s diseases of the newborn, ed 6, Philadelphia, 1991, WB Saunders.)
The basic defect requiring treatment in RDS is inadequate pulmonary exchange of oxygen and carbon dioxide; metabolic acidosis and circulatory insufficiency are secondary manifestations. Early supportive care of premature infants, especially in the treatment of acidosis, hypoxia, hypotension (see Chapter 98), and hypothermia, may lessen the severity of RDS. Therapy requires careful and frequent monitoring.
Another approach is to improve oxygenation and ventilation–perfusion matching. CPAP reduces collapse of surfactant-deficient alveoli and improves both FRC and ventilation–perfusion matching. Early use of CPAP for stabilization of at-risk preterm infants beginning as early as in the delivery room reduces ventilatory needs. Another approach is to intubate the preterm infant, administer intratracheal surfactant and then extubate the infant and begin CPAP. The amount of CPAP required usually decreases after approximately 72 hr of age, and most infants can be weaned from CPAP shortly thereafter. If an infant with RDS undergoing CPAP cannot keep oxygen saturation >90% while breathing 40-70% oxygen, assisted ventilation and surfactant are indicated.

Infants with respiratory failure or persistent apnea require assisted mechanical ventilation. Reasonable measures of respiratory failure are: (1) arterial blood pH <7.20, (2) arterial blood Pco2 of 60 mm Hg or higher, and (3) oxygen saturation <90% at oxygen concentrations of 40-70% and CPAP of 5-10 cm H2O. Infants with persistent apnea also need mechanical ventilation. Intermittent positive pressure ventilation delivered by time-cycled, pressure-limited, continuous flow ventilators is a common method of conventional ventilation for newborns. Other methods of conventional ventilation are synchronized intermittent mandatory ventilation (the set rate and pressure synchronized with the patient's own breaths), pressure support (the patient triggers each breath and a set pressure is delivered), and volume ventilation (a mode in which a specific tidal volume is set and the delivered pressure varies), and combinations thereof. Assisted ventilation for infants with RDS should always include appropriate PEEP (see Chapter 71.1). High ventilatory rates (≥60/min) with lower tidal volumes result in fewer air leaks. With use of high ventilatory rates, sufficient expiratory time should be allowed to avoid the inadvertent PEEP.

The goal of mechanical ventilation is to improve oxygenation and elimination of carbon dioxide without causing pulmonary injury or oxygen toxicity. Acceptable ranges of blood gas values, after the risks of hypoxia and acidosis are balanced against those of mechanical ventilation, vary among institutions: Pao2 50-70 mm Hg, Paco2 45-65 mm

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**Figure 101-5 Infant with respiratory distress syndrome.** Note the granular lungs, air bronchogram, and air-filled esophagus. Anteroposterior (A) and lateral (B) roentgenograms are needed to distinguish the umbilical artery from the vein catheter and to determine the appropriate level of insertion. The lateral view clearly shows that the catheter has been inserted into an umbilical vein and is lying in the portal system of the liver. A indicates endotracheal tube; B indicates the umbilical venous catheter at the junction of the umbilical vein, ductus venosus, and portal vein; C indicates the umbilical artery catheter passed up the aorta to T12. (Courtesy of Walter E. Berdon, Babies Hospital, New York City.)
High-frequency ventilation (HFV) achieves desired alveolar ventilation by using smaller tidal volumes and higher rates (300-1,200 breaths/min) rates (and presumed low vs. high tidal volumes, respectively) revealed that the high ventilatory rate strategy led to fewer air leaks and a trend for increased survival. If mechanical ventilation is needed, a ventilatory approach using small tidal volumes and permissive hypercapnia can be employed. Permissive hypercapnia is a strategy for the management of patients receiving ventilatory support in which priority is given to the prevention or limitation of lung injury from the ventilator by tolerating relatively high levels of PacO₂, rather than maintenance of normal blood gas values. Permissive hypercapnia can be implemented during CPAP and mechanical ventilation. Volume-targeted ventilation allows the clinician to set a tidal volume that may prevent volutrauma. There are limited data on volume-targeted ventilation, but this mode of ventilation may decrease the rates of pneumothorax and BPD.

Hyperoxia may also contribute to lung injury in preterm infants. However, a lower target range of oxygenation (85-89%), as compared with a higher range (91-95%) increases mortality, and does not alter rates of BPD, BPD/death, blindness, or neurodevelopmental impairment. Therefore, the currently recommended range of oxygen saturation targets is 91-95%.

Many ventilated neonates receive sedation or pain relief with benzodiazepines or opiates (morphine, fentanyl), respectively. Midazolam is approved for use in neonates and has demonstrated sedative effects. Adverse hemodynamic effects and myoclonus have been associated with its use in neonates. If midazolam is used, a continuous infusion or administration of individual doses over at least 10 min is recommended to reduce these risks. Data are insufficient to assess the efficacy and safety of lorazepam. Diazepam is not recommended owing to its long half-life, its long-acting metabolites, and concern about the benzyl alcohol content of diazepam injection. Continuous infusion of morphine in VLBW neonates requiring mechanical ventilation does not reduce mortality rates, severe IVH, or periventricular leukomalacia. The need for additional doses of morphine is associated with poor outcome.

High-frequency ventilation (HFV) achieves desired alveolar ventilation by using smaller tidal volumes and higher rates (300-1,200 breaths/min or 5-20 Hz). HFV may improve elimination of carbon dioxide and improve oxygenation in patients who show no response to conventional ventilators and those who have severe RDS, interstitial emphysema, recurrent pneumothoraces, or meconium aspiration pneumonia. High-frequency oscillatory ventilation (HFOV) and high-frequency jet ventilation are the most frequently used methods of HFV. HFOV reduces BPD but may raise the risk for intracranial hemorrhage. HFOV strategies that promote lung recruitment, combined with surfactant therapy, may improve gas exchange. High-frequency jet ventilation facilitates resolution of air leaks. Elective use of either method, in comparison with conventional ventilation, generally does not offer advantages if used as the initial ventilation strategy to treat infants with RDS.

Surfactant deficiency is the primary pathophysiology of RDS. Immediate effects of surfactant replacement therapy include improved alveolar-arterial oxygen gradients, reduced ventilatory support, increased pulmonary compliance, and improved chest radiograph appearance. In neonates with RDS who fail CPAP, treatment with endotracheal surfactant should be initiated immediately after intubation. Repeated dosing is given every 6-12 hr for a total of 2 to 4 doses, depending on the preparation. Exogenous surfactant should be given by a physician who is qualified in neonatal resuscitation and respiratory management. Additional on-site staff support required includes nurses and respiratory therapists experienced in the ventilatory management of preterm infants. Appropriate monitoring equipment (radiology, blood gas laboratory, pulse oximetry) must also be available. Complications of surfactant therapy include transient hypoxia, hypercapnia, bradycardia and hypotension, blockage of the endotracheal tube, and pulmonary hemorrhage (see Chapter 101.13).

A number of surfactant preparations are available, including synthetic surfactants and natural surfactants derived from animal sources. The lack of reduction in BPD rates following surfactant replacement is probably, in part, a result of the survival of infants with severe RDS who would have died without surfactant administration. Infants requiring ventilator support after 1 wk of age may experience transient episodes of surfactant dysfunction associated with deficiencies of SP-B and SP-C, which are temporarily associated with episodes of infection and respiratory deterioration. Surfactant treatment may be beneficial in these infants.

Strategies for weaning infants from ventilators vary widely and are influenced by lung mechanics as well as the availability of ventilatory modes (pressure support). Once extubated, many infants are transitioned to nasal CPAP to avoid postextubation atelectasis and reduce re-intubation. Synchronized nasal intermittent ventilation decreases the need for re-intubation in premature infants. High flow (1-2 L/min) or warmed, humidified high-flow (2-8 L/min) nasal cannula oxygen is commonly used to support term and near-term infants following extubation and to wean premature infants from nasal CPAP. Preloading with methylxanthines may enhance the success of extubation.

Pharmacologic Therapies

Systemic corticosteroids have been used to treat infants with RDS, to selectively treat infants who continue to require respiratory support, and to treat those in whom BPD develops. Mortality and/or BPD at 36 wk decrease with moderately early (7-14 days) administration of corticosteroids. Early (<96 hr) and delayed (>2-3 wk) administration of systemic steroids has also been assessed with meta-analyses, and the results are qualitatively similar. However, there are short-term adverse effects, including hyperglycemia, hypertension, gastrointestinal bleeding, gastrointestinal perforation, hypertrophic obstructive cardiomyopathy, poor weight gain, poor growth of the head, and a trend toward a higher incidence of periventricular leukomalacia. Furthermore, data showing an increased incidence of neurodevelopmental delay and cerebral palsy in infants randomly assigned to receive systemic corticosteroids raise serious concerns about adverse long-term outcomes of this therapy. Thus, routine use of systemic corticosteroids for the prevention or treatment of BPD is not recommended by the Consensus Group of the American Academy of Pediatrics and the Canadian Pediatric Society. Administration of inhaled steroids to ventilated preterm infants during the 1st 2 wk after birth reduced the need for systemic steroids and tended to decrease rates of death and/or BPD at 36 wk without an increase in adverse effects.

Inhaled nitric oxide has been evaluated in preterm infants following the observation of its effectiveness in term and near-term infants with hypoxic respiratory failure. Inhaled nitric oxide (INO) decreases the need for extracorporeal membrane oxygenation (ECMO) in term and near-term infants with hypoxic respiratory failure or persistent pulmonary hypertension of the neonate. Trials in preterm infants report heterogeneous effects on BPD, mortality, and other important outcomes. The most current data do not support the
routine administration of iNO in preterm infants with hypoxemic respiratory failure.

Prevention of extubation failure has been attempted with use of various pharmacologic approaches. Methylxanthines appear to have a large effect on reducing extubation failure. Similarly, use of systemic steroids before extubation reduces the need for reintubation (from 10% to 1%). In contrast, administration of racemic epinephrine after extubation does not improve pulmonary function or the rate of extubation failure.

**Metabolic acidosis** in RDS may be a result of perinatal asphyxia and hypotension and is often encountered when an infant has required prolonged resuscitation (see Chapter 100). Sodium bicarbonate, 1-2 mEq/kg, may be administered over 15-20 min through a peripheral or umbilical vein, followed by an acid–base determination within 30 min, or it may be administered over several hours. Often, sodium bicarbonate is administered on an emergency basis through an umbilical venous catheter. Alkali therapy may result in skin sloughing from infiltration, increased serum osmolarity, hypernatremia, hypocalcemia, hypokalemia, and liver injury when concentrated solutions are administered rapidly through an umbilical venous catheter wedged in the liver.

**Monitoring of aortic blood pressure** through an umbilical or peripheral arterial catheter or by oscillometric technique is useful in managing the shock-like state that may occur during the 1st hr or so in premature infants who have been asphyxiated or have severe RDS (see Fig. 100-2 in Chapter 100). The position of a radiopaque umbilical catheter should be checked radiographically after insertion (see Fig. 101-5). The tip of an umbilical artery catheter should lie at L3-L5 just above the bifurcation of the aorta or at T6-T10. Preferred sites for peripheral catheters are the radial or posterior tibial arteries. The placement and supervision should be carried out by skilled and experienced personnel. Catheters should be removed as soon as patients no longer have any indication for their continued use—usually when an infant is stable and the Fio2 is <40%. Hypotension and low flow in the superior vena cava have been associated with higher rates of CNS morbidity and mortality and should be treated with cautious administration of volume (crystalloid) and early use of vasopressors. Dopamine is more effective in raising blood pressure than dobutamine. Hypotension may be refractory to pressors, but responsive to glucocorticoids, especially in neonates <1,000 g. This hypotension may result from transient adrenal insufficiency in the ill premature infant, which may be treated with intravenous hydrocortisone at 1-2 mg/kg/dose q 6-12 hr (see Chapter 98).

Periodic monitoring of $P_{aO_2}$, $P_{aCO_2}$, and pH is an important part of the management; if assisted ventilation is being used, such monitoring is essential. Oxygenation may be assessed continuously from transcutaneous electrodes or pulse oximetry (oxygen saturation). Capillary blood samples are of limited value for determining $P_{aO_2}$ but may be useful for evaluating $P_{aCO_2}$ and pH.

Because of the difficulty of distinguishing **group B streptococcal** or other bacterial infections from RDS, empirical antibiotic therapy is indicated until the results of blood cultures are available. Penicillin or ampicillin with an aminoglycoside is suggested, although the choice of antibiotics should be based on the recent pattern of bacterial sensitivity in the hospital where the infant is being treated (see Chapter 109).

**COMPLICATIONS OF RESPIRATORY DISTRESS SYNDROME AND INTENSIVE CARE**

The most serious complications of **tracheal intubation** are pneumothorax and other air leaks, asphyxia from obstruction or dislodgment of the tube, bradycardia during intubation or suctioning, and the subsequent development of subglottic stenosis. Other complications include bleeding from trauma during intubation, posterior pharyngeal pseudodiverticula, need for tracheostomy, ulceration of the nares caused by pressure from the tube, permanent narrowing of the nostril as a result of tissue damage and scarring from irritation or infection around the tube, erosion of the palate, avulsion of a vocal cord, laryngeal ulcer, papilloma of a vocal cord, and persistent hoarseness, stridor, or edema of the larynx.

Measures to reduce the incidence of these complications include skillful intubation, adequate securing of the tube, use of polyvinyl endotracheal tubes, use of the smallest tube that will provide effective ventilation in order to reduce local pressure necrosis and ischemia, avoidance of frequent changes and motion of the tube in situ, avoidance of too frequent or too vigorous suctioning, and prevention of infection through meticulous cleanliness and frequent sterilization of all apparatus attached to or passed through the tube. The personnel inserting and caring for the endotracheal tube should be experienced and skilled in such care.

Risks associated with **umbilical arterial catheterization** include vascular embolization, thrombosis, spasm, and vascular perforation; ischemic or chemical necrosis of abdominal viscera; infection; accidental hemorrhage; hypertension; and impairment of circulation to a leg with subsequent gangrene. Aortography has demonstrated that clots form in or about the tips of 95% of catheters placed in an umbilical artery. Aortic ultrasonography can also be used to investigate for the presence of thrombosis. The risk of a serious clinical complication resulting from umbilical catheterization is probably between 2% and 5%.

Transient blanching of the leg may occur during catheterization of the umbilical artery. It is usually caused by reflex arterial spasm, the incidence of which is lessened by using the smallest available catheter, particularly in very small infants. The catheter should be removed immediately; catheterization of the other artery may then be attempted. Persistent spasm after removal of the catheter may be relieved by a small amount of topical nitroglycerin paste applied to the affected area or by warming the other leg. Blood sampling from a radial artery may similarly result in spasm or thrombosis, and the same treatment is indicated. Intermittent severe spasm or unrelieved spasm may respond to the cautious use of topical nitroglycerin. Spasm or thrombosis unresponsive to treatment may result in gangrene of the organ or area supplied by the vessel.

Serious hemorrhage upon removal of the catheter is rare. Thrombi may form in the artery or in the catheter, the incidence of which can be lowered by using a smooth-tipped catheter with a hole only at its end, by rinsing the catheter with a small amount of saline solution containing heparin, or by continuously infusing a solution containing 1-2 units/mL of heparin. The risk of thrombus formation with potential vascular occlusion can also be reduced by removing the catheter when early signs of thrombosis, such as narrowing of pulse pressure and disappearance of the dicrotic notch, are noted. Some authorities prefer to use the umbilical artery for blood sampling only and to leave the catheter filled with heparinized saline between samplings. Renovascular hypertension may occur days to weeks after umbilical arterial catheterization in a small proportion of neonates.

Umbilical vein catheterization is associated with many of the same risks as umbilical artery catheterization. Additional risks are cardiac perforation and pericardial tamponade; portal hypertension can develop from portal vein thrombosis, especially in the presence of omphalitis.

Air leaks are a common complication of the management of infants with RDS (see Chapter 101.12).

Some neonates with RDS may have clinically significant shunting through a PDA. Delayed closure of the PDA is associated with hypoxia, acidosis, increased pulmonary pressure secondary to vasoconstriction, systemic hypotension, immaturity, and local release of prostaglandins, which dilate the ductus. Shunting through the PDA may initially be bidirectional or right-to-left. As RDS resolves, PVR decreases, and left-to-right shunting may occur, leading to left ventricular volume overload and pulmonary edema. Manifestations of PDA may include (1) a hyperdynamic precordium, bounding peripheral pulses, wide pulse pressure, and a continuous or systolic murmur with or without extension into diastole or an apical diastolic murmur, or multiple clicks resembling the shaking of dice; (2) radiographic evidence of cardiomegaly and increased pulmonary vascular markings; (3) hepatomegaly; (4) increasing oxygen dependence; and (5) carbon dioxide retention. The diagnosis is confirmed by echocardiographic visualization of a PDA with Doppler flow imaging that demonstrates left-to-right or
bidirectional shunting. Prophylactic “closure” before signs of a PDA, closure of the asymptomatic but clinically detected PDA, and closure of the symptomatic PDA are 3 strategies to manage a PDA. Interventions include fluid restriction, the use of cyclooxygenase inhibitors (indomethacin or ibuprofen) to close the ductus, and surgical closure. Short-term benefits have to be balanced against adverse effects such as transient renal dysfunction and a possible increase in the risk of intestinal perforation with indomethacin. Much uncertainty about “best practice” in the management of a PDA remains. Many cases respond to general supportive measures, including fluid restriction. Medical and/or surgical ductus closure is indicated in the premature infant with a large PDA when there is a delay in clinical improvement or deterioration after initial clinical improvement of RDS. Intravenous indomethacin (0.1–0.2 mg/kg/dose) is given in 3 doses every 12–24 hr; treatment may be repeated once. A second course may be needed in a few symptomatic patients. If closure does not occur in a symptomatic patient, surgical ligation is usually the next step. Prophylactic low-dose indomethacin given soon after birth reduces the incidence of both IVH and PDA and improves the rate of permanent ductus closure even in the most immature infants. Contraindications to indomethacin include thrombocytopenia (<50,000 platelets/mm³), bleeding disorders, oliguria (urine output <1 mL/kg/hr), necrotizing enterocolitis, isolated intestinal perforation, and an elevated plasma creatinine value (>1.8 mg/dL). The infant whose symptomatic PDA fails to close with indomethacin or who has contraindications to indomethacin is a candidate for surgical closure. Surgical mortality is very low even in the extremely low-birthweight infants. Complications of surgery include Horner syndrome, injury to the recurrent laryngeal nerve, chylothorax, transient hypertension, pneumothorax, and bleeding from the surgical site. Inadvertent ligation of the left pulmonary artery or the transverse aortic arch has rarely been reported.

Intravenous ibuprofen may be an alternative to indomethacin; it can be as effective in closing a PDA without reducing cerebral, mesenteric, or renal blood flow velocity. Compared with indomethacin, therapeutic ibuprofen has a lower risk of oliguria.

BPD is a result of lung injury in infants requiring mechanical ventilation and supplemental oxygen. The clinical, radiographic, and lung histology of classic BPD described in 1967, in an era before the widespread use of antenatal steroids and postnatal surfactant, was that of a disease of more mature preterm infants with RDS who were treated with positive-pressure ventilation and oxygen. The new BPD is a disease primarily of infants with birthweight <1,000 g who were born at <28 wk of gestation, some of whom have little or no lung disease at birth but experience progressive respiratory failure over the 1st few wk of life.

The lung histology currently found in infants with the new BPD include alveolar hyalinosis, variable saccular wall fibrosis, and minimal airway disease. Some specimens also have decreased pulmonary microvasculature development. The histopathology of BPD indicates interference with normal alveolar septation and microvascular maturation, which may prevent subsequent lung growth and development. The pathogenesis of BPD is multifactorial and affects both the lungs and the heart. RDS is a disease of progressive alveolar collapse. Alveolar collapse (atelectrauma) as a consequence of surfactant deficiency, together with ventilator-induced phasic overdistention of the lung (volutrauma), promotes injury. Oxygen induces injury by producing free radicals that cannot be metabolized by the immature antioxidant systems of VLBW neonates. Mechanical ventilation and oxygen injure the lung through their effect on alveolar and vascular development. Inflammation (detected with measurement of circulating neutrophils, neutrophils and macrophages in alveolar fluid, and proinflammatory cytokines) contributes to the progression of lung injury. Several clinical factors, including immaturity, chorioamnionitis, infection, symptomatic PDA, and malnutrition, contribute to the development of BPD.

The occurrence of BPD is inversely related to gestational age. Additional associations include the presence of interstitial emphysema, male sex, low PaO₂ during the treatment of RDS, PDA, high peak inspiratory pressure, increased airway resistance in the 1st wk of life, increased pulmonary artery pressure, and, possibly, a family history of atopy or asthma. Genetic polymorphisms may increase the risk for development of BPD. In some VLBW infants without RDS who require mechanical ventilation for apnea or respiratory insufficiency, BPD that does not follow the classic pattern may develop. Overhydration during the 1st days of life may also contribute to the development of BPD.

Vitamin A supplementation (5,000 IU intramuscularly 3 times/wk for 4 wk) in VLBW infants reduces the risk of BPD (1 case prevented for every 14–15 infants treated). Early use of nasal CPAP and rapid extubations with transition to nasal CPAP are associated with a decreased risk of BPD.

Instead of showing improvement on the 3rd or 4th day, which would be consistent with the natural course of RDS, some infants demonstrate an increased need for oxygen and ventilatory support. Respiratory distress persists or worsens and is characterized by hypoxia, hypercapnia, oxygen dependence, and, in severe cases, the development of right-sided heart failure. The chest radiograph may reveal pulmonary interstitial emphysema, wandering atelectasis with concomitant hyperinflation, and cyst formation (Fig. 101-6). Four distinct pathologic stages of classic BPD have been identified: acute lung injury, exudative bronchiolitis, proliferative bronchiolitis, and obliterative fibroproliferative bronchiolitis. Histologic study at this stage (10–20 days) shows residual hyaline membrane formation, progressive alveolar coalescence with atelectasis of the surrounding alveoli, interstitial edema, coarse focal thickening of the basement membrane, and widespread bronchial and bronchiolar mucosal metaplasia and hyperplasia. These findings correspond to a severe maldistribution of ventilation. Pathologic examination of infants who die later in the course of BPD reveals cardiac enlargement and pulmonary changes consisting of focal areas of emphysema with hypertrophy of the peribronchial smooth muscle of the tributary bronchioles, perimucosal fibrosis, widespread metaplasia of the bronchiolar mucosa, thickening of basement membranes, and separation of the capillaries from the alveolar epithelial cells.

BPD can be classified according to the need for oxygen supplementation (Table 101-2). Neonates receiving positive pressure support or ≥30% supplemental oxygen at 36 wk or at discharge (whichever occurs first) are diagnosed as having severe BPD. Those needing supplementation with 22–29% oxygen at this age are diagnosed as having moderate BPD. Those who need oxygen supplementation for >28 days but are breathing room air at 36 wk or at discharge are diagnosed as having mild BPD. Those receiving <30% oxygen should undergo a stepwise 2% reduction in supplemental oxygen to room air while under continuous observation and with oxygen saturation monitoring to determine whether they can be weaned off oxygen (physiologic definition of BPD). This test is highly reliable and correlated with discharge home on oxygen, length of hospital stay, and hospital readmissions in the 1st yr of life.

Severe BPD requires prolonged mechanical ventilation. Gradual weaning should be attempted despite elevations in PaCO₂, because hypercapnia may be the result of gas trapping rather than inadequate minute ventilation. Acceptable blood gas concentrations include hypercapnia with pH >7.20 and a PaO₂ of 50–70 mm Hg with an oxygen saturation of 91–95%. Lower levels of PaO₂ may exacerbate pulmonary hypertension with resultant cor pulmonale, so the lower limit of oxygenation targets in neonates with BPD are higher than those in neonates with RDS. Airway obstruction in BPD may be due to mucus and edema production, bronchospasm, and airway collapse from acquired tracheobronchomalacia. These events may contribute to “blue spells.” Alternatively, blue spells may be the result of acute pulmonary vasospasm or right ventricular dysfunction.

Treatment of BPD includes nutritional support, fluid restriction, drug therapy, maintenance of adequate oxygenation, and prompt treatment of infection. Growth must be monitored because recovery depends on the growth of lung tissue and remodeling of the pulmonary vascular bed. Nutritional supplementation to provide added calories (24–30 calories/30 mL formula), protein (3–3.5 g/kg/24 hr), and fat (3 g/kg/24 hr) is needed for growth. Diuretic therapy results in a short-term improvement in lung mechanics and may lead to decreased oxygen and ventilatory requirements. Furosemide (1 mg/kg/dose...
Figure 101-6 Pulmonary changes in infants treated with prolonged, intermittent positive-pressure breathing with air containing 80-100% oxygen in the immediate postnatal period for the clinical syndrome of hyaline membrane disease. A, A 5 day old infant with nearly complete opacification of the lungs. B, A 13 day old infant with “bubbly lungs” simulating the roentgenographic appearance of the Wilson-Mikity syndrome. C, A 7 mo old infant with irregular, dense strands in both lungs, hyperinflation, and cardiomegaly suggestive of chronic lung disease. D, Large right ventricle and a cobbly, irregular aerated lung of an infant who died at 11 mo of age. This infant also had a PDA. (From Northway WH Jr, Rosan RC, Porter DY: Pulmonary disease following respirator therapy of hyaline-membrane disease, N Engl J Med 276:357–368, 1967.)

Table 101-2  Definition of BPD: Diagnostic Criteria

<table>
<thead>
<tr>
<th>GESTATIONAL AGE</th>
<th>&lt;32 Wk</th>
<th>≥32 Wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time point of assessment</td>
<td>36 wk postmenstrual age or discharge home, whichever comes first</td>
<td>&gt;28 days but &lt;56 days postnatal age or discharge home, whichever comes first</td>
</tr>
<tr>
<td>Treatment with &gt;21% oxygen for at least 28 days plus</td>
<td>Treatment with &gt;21% oxygen for at least 28 days plus</td>
<td></td>
</tr>
<tr>
<td>Mild BPD</td>
<td>Breathing room air at 36 wk postmenstrual age or discharge home, whichever comes first</td>
<td>Breathing room air by 56 days postnatal age or discharge home, whichever comes first</td>
</tr>
<tr>
<td>Moderate BPD</td>
<td>Need¹ for &lt;30% oxygen at 36 wk postmenstrual age or discharge home, whichever comes first</td>
<td>Need¹ for &lt;30% oxygen at 56 days postnatal age or discharge home, whichever comes first</td>
</tr>
<tr>
<td>Severe BPD</td>
<td>Need¹ for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 36 wk postmenstrual age or discharge home, whichever comes first</td>
<td>Need¹ for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 56 days postnatal age or discharge home, whichever comes first</td>
</tr>
</tbody>
</table>

*BPD usually develops in neonates being treated with oxygen and PPV for respiratory failure, most commonly respiratory distress syndrome. Persistence of the clinical features of respiratory disease (tachypnea, retractions, crackles) is considered common to the broad description of BPD and has not been included in the diagnostic criteria describing the severity of BPD. Infants treated with >21% oxygen and/or PPV for nonrespiratory disease (e.g., central apnea or diaphragmatic paralysis) do not have BPD unless parenchymal lung disease also develops and they have clinical features of respiratory distress. A day of treatment with >21% oxygen means that the infant received >21% oxygen for more than 12 hr on that day. Treatment with >21% oxygen and/or PPV at 36 wk postmenstrual age or at 56 days postnatal age or discharge should not reflect an “acute” event, but should rather reflect the infant’s usual daily therapy for several days preceding and after 36 wk postmenstrual age, 56 days postnatal age, or discharge.

¹A physiologic test confirming that the oxygen requirement at the assessment time point remains to be defined. This assessment may include a pulse oximetry saturation range.


intravenously twice daily [bid] or 2 mg/kg/dose orally bid) is the treatment of choice for acute fluid overload in infants with BPD. This loop diuretic has been demonstrated to decrease pulmonary interstitial emphysema and PVR, improve pulmonary function, and facilitate weaning from mechanical ventilation and oxygen. Adverse effects of long-term diuretic therapy are common and include hyponatremia, hypokalemia, alkalosis, azotemia, hypocalcemia, hypercalciumia, cholelithiasis, renal stones, nephrocalcinosis, and ototoxicity. Potassium chloride supplementation is often necessary. Hyponatremia should be treated with fluid restriction and a decrease in the dose or frequency of furosemide. Thiazide diuretics have been used in infants with BPD. Several trials of thiazide diuretics combined with spironolactone have
shown increased urine output with or without improvement in pulmonary mechanics in infants with BPD. Adverse effects include electrolyte imbalance.

Inhaled bronchodilators improve lung mechanics by decreasing airway resistance. Albuterol is a specific β₂-agonist used to treat bronchospasm in infants with BPD. Albuterol may improve lung compliance by decreasing airway resistance secondary to smooth muscle cell relaxation. Changes in pulmonary mechanics may last as long as 4-6 hr. Adverse effects include hypertension and tachycardia. Ipratropium bromide is a muscarinic antagonist related to atropine, but with more potent bronchodilator effects. Improvements in pulmonary mechanics have been demonstrated in BPD after ipratropium bromide inhalation. Combination therapy using albuterol and ipratropium bromide may be more effective than either agent alone. Few adverse effects have been noted. With current aerosol administration strategies, exactly how much medication is delivered to the airways and lungs of infants with BPD, especially if they are ventilator dependent, is unclear. Because significant smooth muscle relaxation does not appear to occur within the 1st few wk of life, aerosol therapy in the early stages of BPD is not indicated. Methylxanthines are used to increase respiratory drive, decrease apnea, and improve diaphragmatic contractility. Methylxanthines may also decrease PVR and increase lung compliance in infants with BPD, probably through direct smooth muscle relaxation. They also exhibit diuretic effects. These effects may accelerate weaning from mechanical ventilation. Synergy between theophylline and diuretics has been demonstrated. Theophylline has a half-life of 30-40 hr, is metabolized primarily to caffeine in the liver and may have adverse effects, such as tachycardia, gastrointestinal bleeding and perforation, hypertrophic cardiomyopathy, seizures, and poor weight gain and head growth. Survival is not improved, and infants who have been treated with dexamethasone have an increased risk of neurodevelopmental delay and cerebral palsy. The use of dexamethasone for the prevention of BPD is not recommended unless an infant has severe pulmonary disease, for example is ventilator dependent for at least 1 to 2 wk after birth. A rapid tapering course of therapy, starting at 0.25 mg/kg/day and lasting for 5-7 days, may be adequate. Inhaled beclomethasone does not prevent BPD but does decrease the need for systemic steroids. Inhaled corticosteroids facilitate earlier extubation of ventilated infants with BPD.

Physiologic abnormalities of the pulmonary circulation in BPD include elevated PVR and abnormal vasoreactivity. Acute exposure to even modest levels of hypoxemia causes large elevations in pulmonary artery pressure in infants with BPD with pulmonary hypertension. Higher oxygen saturations are effective in lowering pulmonary artery pressure. The current recommendation for treatment of patients with BPD and pulmonary hypertension is to maintain oxygen saturation values in the 91-95% range.

Low-dose iNO has no acute effects on lung function, cardiac function, or oxygenation in evolving BPD. The use of low-dose iNO may improve oxygenation in some infants with severe BPD, allowing decreased FiO₂ and ventilator support.

**PROGNOSIS**

Early provision of intensive observation and care of high-risk newborn infants can significantly reduce the morbidity and mortality associated with RDS and other acute neonatal illnesses. Antenatal steroids, postnatal surfactant use, and improved modes of ventilation have resulted in low mortality from RDS (<10%). Mortality increases with decreasing gestational age. Optimal results depend on the availability of experienced and skilled personnel, care in specially designed and organized regional hospital units, proper equipment, and lack of complications such as severe asphyxia, intracranial hemorrhage, or irreducible congenital malformation. Surfactant therapy has reduced mortality from RDS by approximately 40%, but the incidence of BPD has not been measurably affected.

Although 85-90% of all infants surviving RDS after requiring ventilatory support with respirators are normal, the outlook is much better for those weighing >1,500 g. The long-term prognosis for normal pulmonary function in most infants surviving RDS is excellent. Survivors of severe neonatal respiratory failure may have significant pulmonary and neurodevelopmental impairment.

Prolonged ventilation, ICH, pulmonary hypertension, cor pulmonale, and oxygen dependence beyond 1 yr of life are poor prognostic signs. Mortality in infants with BPD ranges from 10-25% and is highest in infants who remain ventilator dependent for longer than 6 mo. Cardiorespiratory failure associated with cor pulmonale and acquired infection (respiratory syncytial virus) are common causes of death. Survivors with BPD often go home on a regimen of oxygen, diuretics, and bronchodilator therapy.

Pulmonary function slowly improves in most survivors owing to continued lung and airway growth and healing. Rehospitalization for impaired pulmonary function is most common during the 1st 2 yr of life. There is a gradual decrease in symptom frequency in children ages 6-9 yr from the frequency during the 1st 2 yr of life. Persistence of respiratory symptoms and abnormal pulmonary function test results are present in children ages 7-10 yr. Pulmonary function testing in children with a history of BPD shows persistent abnormalities in clinical moderate expiratory flow obstruction. Approximately 25-50% of very-low birthweight infants and more than 50% of children born at less than 26 wk of gestation continue to have abnormal spirometry as preadolescents. Many have asthma and respond to bronchodilators. Infants are at risk for severe respiratory syncytial virus infections and must receive prophylactic therapy (see Chapter 260). Airway obstruction and hyperactivity and hyperinflation are noted in some adolescent and adult survivors of BPD. High-resolution chest CT scanning or MRI studies in children and adults with a history of BPD reveal lung abnormalities that correlate directly with the degree of pulmonary function abnormality.

Noncardiorespiratory complications of BPD include growth failure, psychomotor retardation, and parental stress, as well as sequelae of therapy, such as nephrolithiasis, osteopenia, and electrolyte imbalance. Airway problems, such as tonsillar and adenoidal hypertrophy, vocal cord paralysis, subglottic stenosis, and tracheomalacia, are common and may aggravate or cause pulmonary hypertension. Subglottic stenosis may require tracheotomy or an anterior cricoid split procedure to relieve upper airway obstruction. Cardiac complications of BPD include pulmonary hypertension, cor pulmonale, systemic hypertension, left ventricular hypertrophy, and the development of aortopulmonary collateral vessels, which, if large, may cause heart failure.

**Bibliography is available at Expert Consult.**

### 101.4 Transient Tachypnea of the Newborn

Namasivayam Ambalavanan and Waldemar A. Carlo

Transient tachypnea is most common after term cesarean delivery. It is characterized by the early onset of tachypnea, sometimes with retractions, or expiratory grunting and, occasionally, cyanosis that is relieved by minimal oxygen supplementation (<40%). Most infants recover rapidly, usually within 3 days. The chest generally sounds clear without crackles or wheeze, and the chest radiograph shows prominent pulmonary vascular markings, fluid in the intralobular fissures, overaeration, flat diaphragms, and, rarely, small pleural effusions. Hypercapnia and acidosis are uncommon. Distinguishing the disease from RDS and other respiratory disorders (e.g., pneumonia) may be difficult, and transient tachypnea is frequently a diagnosis of exclusion; the distinctive features of transient tachypnea are rapid recovery of the infant and the absence of radiographic findings for RDS (hypoaeration, diffuse reticulogranular pattern, air bronchograms) and other lung disorders. The syndrome is believed to be secondary to slow absorption of fetal


lungs fluid, resulting in decreased pulmonary compliance and tidal volume and increased dead space. In severe cases, retained fetal lung fluid may interfere with the normal postnatal fall in PVR, resulting in persistent pulmonary hypertension; a mild surfactant deficiency may be present. Treatment is supportive. There is no evidence supporting the use of oral furosemide or racemic epinephrine in this disorder. One study demonstrated efficacy of inhaled salbutamol in enhancing resolution of transient tachypnea of the newborn.

Severe respiratory morbidity and mortality have been reported in infants born by elective cesarean section before full term (late preterm infants) who initially present with signs and symptoms of transient tachypnea. These infants often demonstrate refractory hypoxemia as a result of pulmonary hypertension and require ECMO support. The term “malignant transient tachypnea of the newborn” has been used to describe this condition. The initial approach to these infants is similar to that of RDS plus the concern for pulmonary hypertension.

Bibliography is available at Expert Consult.

101.5 Aspiration of Foreign Material (Fetal Aspiration Syndrome, Aspiration Pneumonia)
Waldemar A. Carlo

With fetal distress, infants often initiate vigorous respiratory movements in utero because of interference with the supply of oxygen through the placenta. Under such circumstances, the infant may aspirate amniotic fluid containing vernix caseosa, epithelial cells, meconium, blood, or material from the birth canal, which may block the smallest airways and interfere with alveolar exchange of oxygen and carbon dioxide. Pathogenic bacteria may accompany the aspirated material, and pneumonia may ensue, but even in noninfected cases, respiratory distress accompanied by radiographic evidence of aspiration is seen (Fig. 101-7).

Postnatal pulmonary aspiration may also occur in newborn infants as a result of prematurity, tracheoesophageal fistula, esophageal and duodenal obstruction, gastroesophageal reflux, improper feeding practices, and administration of depressant medicines. To avoid aspiration of gastric contents, the stomach should be aspirated using a soft catheter just before surgery or other major procedures that require anesthesia or conscious sedation. The treatment of aspiration pneumonia is symptomatic and may include respiratory support and systemic antibiotics (see Chapters 109.8 and 397). Gradual improvement generally occurs over 3-4 days.

101.6 Meconium Aspiration
Namasivayam Ambalavanan and Waldemar A. Carlo

Meconium-stained amniotic fluid is found in 10-15% of births and usually occurs in term or postterm infants. Meconium aspiration syndrome (MAS) develops in 5% of such infants; 30% require mechanical ventilation and 3-5% die. Usually, but not invariably, fetal distress and hypoxia occur before the passage of meconium into amniotic fluid. The infants are meconium stained and may be depressed and require resuscitation at birth. Figure 101-8 shows the pathophysiology of the MAS. Infants with MAS are at increased risk of persistent pulmonary hypertension (see Chapter 101.7).

CLINICAL MANIFESTATIONS
Either in utero or with the first breath, thick, particulate meconium is aspirated into the lungs. The resulting small airway obstruction may produce respiratory distress within the first hours, with tachypnea, retractions, grunting, and cyanosis observed in severely affected infants. Partial obstruction of some airways may lead to pneumomediastinum, pneumothorax, or both. Overdistention of the chest may be prominent. The condition usually improves within 72 hr, but when its course requires assisted ventilation, it may be severe with a high risk for mortality. Tachypnea may persist for many days or even several weeks. The typical chest radiograph is characterized by patchy infiltrates, coarse streaking of both lung fields, increased anteroposterior diameter, and flattening of the diaphragm. A normal chest roentgenogram in an infant with severe hypoxemia and no cardiac malformation suggests the diagnosis of pulmonary hypertension (see Chapter 101.7).

PREVENTION
The risk of meconium aspiration may be decreased by rapid identification of fetal distress and initiation of prompt delivery in the presence of late fetal heart rate deceleration or poor beat-to-beat fetal heart rate variability. Despite initial enthusiasm for amnioinfusion, it does not reduce the risk of MAS, cesarean delivery, or other major indicators of maternal or neonatal morbidity. Intrapartum nasopharyngeal suctioning in infants with meconium-stained amniotic fluid does not reduce the risk for MAS.

TREATMENT
Routine intubation to aspirate the lungs of vigorous infants born through meconium-stained fluid is not effective in reducing the MAS or other major adverse outcomes. Depressed infants (those with hypotonia, bradycardia, or decreased respiratory effort) are at higher risk of MAS and may benefit from endotracheal intubation and suction to remove meconium from the airway before the first breath in the delivery room, but the data are inconclusive.

Treatment of the MAS includes supportive care and standard management for respiratory distress. The beneficial effect of mean airway pressure on oxygenation must be weighed against the risk of
Bibliography


### 101.7 Persistent Pulmonary Hypertension of the Newborn (Persistent Fetal Circulation)

Namasivayam Ambalavanan and Waldemar A. Carlo

Persistent pulmonary hypertension of the newborn (PPHN) occurs mostly in term and postterm infants. Predisposing factors include birth asphyxia, MAS, early-onset sepsis, RDS, hypoglycemia, polycythemia, maternal use of nonsteroidal antiinflammatory drugs with in utero constriction of the ductus arteriosus, maternal late trimester use of selective serotonin reuptake inhibitors, and pulmonary hypoplasia caused by diaphragmatic hernia, amniotic fluid leak, oligohydramnios, or pleural effusions. PPHN is often idiopathic. Some patients with PPHN have low plasma arginine and NO metabolite concentrations and polymorphisms of the carbamoyl phosphate synthase gene, findings suggestive of a possible subtle defect in NO production. The incidence is 1/500-1,500 live births with a wide variation among clinical centers.

#### PATHOPHYSIOLOGY

Persistence of the fetal circulatory pattern of right-to-left shunting through the PDA and foramen ovale after birth is a result of excessively high PVR. Fetal PVR is usually elevated relative to fetal systemic or postnatal pulmonary pressure. This fetal state normally permits shunting of oxygenated umbilical venous blood to the left atrium (and brain) through the foramen ovale, from which it bypasses the lungs through the ductus arteriosus and passes to the descending aorta. After birth, PVR normally declines rapidly as a consequence of vasodilation secondary to lung inflation, a rise in postnatal PaO₂, a reduction in PaCO₂, increased pH, and release of vasoactive substances. Increased neonatal PVR may be (1) maladaptive from an acute injury (not demonstrating normal vasodilation in response to increased oxygen and other changes after birth); (2) the result of increased pulmonary artery medial muscle thickness and extension of smooth muscle layers into the usually nonmuscular, more peripheral pulmonary arteries in response to chronic fetal hypoxia; (3) a consequence of pulmonary hypoplasia (diaphragmatic hernia, Potter syndrome); or (4) obstructive as a result of polycythemia or total anomalous pulmonary venous return, or of alveolar capillary dysplasia, which is a lethal autosomal recessive disorder characterized by thickened alveolar septa, increased muscularization of the pulmonary arteries, a reduced number of capillaries, and misalignment of the intrapulmonary veins. Regardless of etiology, profound hypoxemia from right-to-left shunting and normal or elevated Paco₂ are present (Fig. 101.9).

#### CLINICAL MANIFESTATIONS

Infants with PPHN usually become ill in the delivery room or within the 1st 12 hr after birth. PPHN related to polycythemia, idiopathic...
Bibliography


causes, hypoglycemia, hypothermia, or asphyxia may result in severe cyanosis with tachypnea, although initial signs of respiratory distress may be minimal. Infants who have PPHN associated with meconium aspiration, group B streptococcal pneumonia, diaphragmatic hernia, or pulmonary hypoplasia usually exhibit cyanosis, grunting, flaring, retractions, tachycardia, and shock. Multigorgan involvement may be present (see Table 98-1 in Chapter 98). Myocardial ischemia, papillary muscle dysfunction with mitral and tricuspid regurgitation, and biventricular dysfunction produce cardiogenic shock with decreases in pulmonary blood flow, tissue perfusion, and oxygen delivery. The hypoxemia is often labile and out of proportion to the findings on chest radiographs.

DIAGNOSIS

PPHN should be suspected in all term infants who have cyanosis independent of a history of fetal distress, intratracheal growth restriction, meconium-stained amniotic fluid, hypoglycemia, polycythemia, diaphragmatic hernia, pleural effusions, or birth asphyxia. Hypoxemia is universal and is at least intermittently unresponsive to 100% oxygen given by oxygen hood, but it may respond transiently to hyperoxic hyperventilation administered after endotracheal intubation or to the application of a bag and mask. A PaO₂ or oxygen saturation gradient between a preductal (right radial artery) and a postductal (umbilical artery) site of blood sampling suggests right-to-left shunting through the ductus arteriosus. Foramen ovale shunting does not lead to a PaO₂ or oxygen saturation gradient.

Real-time echocardiography combined with Doppler flow imaging is very helpful in evaluating PPHN. Systolic flattening of the intraventricular septum as the right ventricular systolic pressure approaches the left ventricular systolic pressure can be used to estimate the degree of pulmonary hypertension. The peak velocity of the tricuspid valve regurgitation jet, when present, yields a quantitative estimate of the right ventricular systolic pressure. Likewise, the direction and velocity of a shunt across the PDA provides a quantitative comparison between the aortic and pulmonary artery pressures. In advanced cases, right-to-left or bidirectional shunting across a PDA and/or a patent foramen ovale can be observed.

In asphyxia-associated and idiopathic PPHN, chest x-ray findings are normal, whereas in PPHN associated with pneumonia and diaphragmatic hernia, parenchymal opacification and bowel and/or liver in the chest, respectively, are seen. The differential diagnosis of PPHN includes cyanotic heart disease (especially obstructed total anomalous pulmonary venous return) congenital surfactant deficiency syndromes, alveolar-capillary dysplasia, and the associated etiologic entities that predispose to PPHN (hypoglycemia, polycythemia, sepsis, hypothermia).

TREATMENT

Therapy is directed toward correcting any predisposing condition (hypoglycemia, polycythemia, others) and improving poor tissue oxygenation. The response to therapy is often unpredictable, transient, and complicated by the adverse effects of drugs or mechanical ventilation. Initial management includes oxygen administration and correction of acidosis, hypotension, and hypercapnia. Persistent hypoxemia should be managed with intubation and mechanical ventilation.

The optimal approach to mechanical ventilation has evolved. In the pre-iNO era, treatment of severe PPHN consisted of instituting mechanical ventilation with 1 or more of the following: muscle relaxants, hyperventilation, and alkalinization with sodium bicarbonate. These therapies may lead to complications associated with hypocarbia including reduced cerebral blood flow, cerebral palsy, and deafness; volutrauma; and impaired cardiac function which have resulted in less use of these practices. Currently, infants with PPHN are usually managed without hyperventilation and/or alkalinization. In skilled hands, “gentle ventilation” with normocarbia or permissive hypercarbia and avoidance of hypoxemia result in excellent outcomes and a low incidence of chronic lung disease and ECMO use.

Because of their instability and ability to fight the ventilator, newborns with PPHN usually require sedation. The use of paralytic agents is controversial and reserved for the newborn that cannot be treated with sedatives alone. Muscle relaxants may promote atelectasis of dependent lung regions and ventilation–perfusion mismatch and may be associated with an increased risk of death.

Inotropic therapy is frequently needed to support blood pressure and perfusion. Whereas dopamine is frequently used as a first-line agent, other agents, such as dobutamine, epinephrine, and milrinone may be helpful when myocardial contractility is poor. Some of the sickest newborns with PPHN demonstrate hypotension refractory to vasopressor administration. This results from desensitization of the cardiovascular system to catecholamines by overwhelming illness and relative adrenal insufficiency. Hydrocortisone rapidly upregulates cardiovascular adrenergic receptor expression and serves as a hormone substitute in cases of adrenal insufficiency.

NO is an endothelium-derived signaling molecule that relaxes vascular smooth muscle and can be delivered to the lung by inhalation. Use of iNO reduces the need for ECMO support by approximately 40%. The optimal starting dose is 20 ppm. Higher doses have not been shown to be more effective and are associated with side effects including methemoglobinemia and increased levels of nitrogen dioxide, a pulmonary irritant. Most newborns require iNO for <5 days. Although NO has been used as long-term therapy in children and adults with primary pulmonary hypertension, prolonged dependency is rare in neonates and suggests the presence of lung hypoplasia, congenital heart disease, or alveolar capillary dysplasia. The maximal safe duration of iNO therapy is unknown. The dose can be weaned to 5 ppm after 6-24 hr of therapy. The dose can then be weaned slowly and discontinued when the FiO₂ is <0.6 and the iNO dose is 1 ppm. Abrupt discontinuation should be avoided as it may cause rebound pulmonary hypertension. iNO should be used only at institutions that offer ECMO support or have the capability of transporting an infant on iNO therapy if a referral for ECMO is necessary. Some infants with PPHN do not respond adequately to iNO. Therapy with continuous inhaled or intravenous prostacyclin (prostaglandin I₂) has improved oxygenation and outcome in infants with PPHN. The safety and efficacy of sildenafil (a type 5 phosphodiesterase inhibitor) in newborns with PPHN is under investigation; initial results are promising.

Extracorporeal Membrane Oxygenation

In 5-10% of patients with PPHN, the response to 100% oxygen, mechanical ventilation, and drugs is poor. In such patients, two parameters have been used to predict mortality, the alveolar-arterial oxygen gradient (PaO₂−PaO₂), and the oxygenation index, which is calculated as follows: FiO₂ (as %) × MAP/PaO₂.

An alveolar–arterial gradient >620 for 8-12 hr and an oxygenation index >40 that is unresponsive to iNO predict a high mortality rate (≥80%) and are indications for ECMO. ECMO is used to treat carefully selected, severely ill infants with hypoxemic respiratory failure caused by RDS, meconium aspiration pneumonia, congenital diaphragmatic hernia, PPHN, or sepsis.

ECMO is a form of cardiopulmonary bypass that augments systemic perfusion and provides gas exchange. Most experience has been with venoarterial bypass, which requires carotid artery ligation and the placement of large catheters in the right internal jugular vein and carotid artery. Venovenous bypass avoids carotid artery ligation and provides gas exchange, but it does not support cardiac output. Blood is initially pumped through the ECMO circuit at a rate that approximates 80% of the estimated cardiac output, 150-200 mL/kg/min. Venous return passes through a membrane oxygenator, is rewarmed, and returns to the aortic arch in venoarterial ECMO and to the right atrium in venovenous ECMO. Venous oxygen saturation values are used to monitor tissue oxygen delivery and subsequent extraction for infants undergoing venoarterial ECMO, whereas arterial oxygen saturation values are used to monitor oxygenation for infants receiving venovenous ECMO.

Because ECMO requires complete heparinization to prevent clotting in the circuit, it cannot be used in patients with or at high risk for IVH (weight <2 kg, gestational age <34 wk). In addition, infants for whom ECMO is being considered should have reversible lung
disease, no signs of systemic bleeding, an absence of severe asphyxia or lethal malformations, and they should have been ventilated for less than 10 days. Complications of ECMO include thromboembolism, air embolization, bleeding, stroke, seizures, atelectasis, cholestatic jaundice, thrombocytopenia, neutropenia, hemolysis, infectious complications of blood transfusions, edema formation, and systemic hypertension.

**PROGNOSIS**

Survival in patients with PPHN varies with the underlying diagnosis. The long-term outcome for infants with PPHN is related to the associated hypoxic-ischemic encephalopathy and the ability to reduce PVR. The long-term prognosis for infants who have PPHN and who survive after treatment with hyperventilation is comparable to that for infants who have underlying illnesses of equivalent severity (birth asphyxia, hypoglycemia, polycythemia). The outcome for infants with PPHN who are treated with ECMO is also favorable; >80-90% survive, and 60-75% of survivors appear normal at 1-3.5 yr of age. Survival of infants born with congenital diaphragmatic hernia (CDH) has increased over the past 10 yr to 67%; benchmark institutions are reporting survival rates >80%. Those infants with CDH who require ECMO continue to have a lower survival than the general neonatal population undergoing ECMO (~50%).

Bibliography is available at Expert Consult.

**101.8 Diaphragmatic Hernia**

*Akhil Maheshwari and Waldemar A. Carlo*

A diaphragmatic hernia is defined as a communication between the abdominal and thoracic cavities with or without abdominal contents in the thorax (Fig. 101-10). The etiology is usually congenital but may be traumatic. The symptoms and prognosis depend on the location of the defect and associated anomalies. The defect may be at the esophageal hiatus (hiatal), paraesophageal (adjacent to the hiatus), retrosternal (Morgagni), or at the posterolateral (Bochdalek) portion of the diaphragm. The term congenital diaphragmatic hernia typically refers to the Bochdalek form. These lesions may cause significant respiratory distress at birth, can be associated with other congenital anomalies, and have significant mortality and long-term morbidity. The overall survival from the CDH Study Group is 67%. The Bochdalek hernia accounts for up to 90% of the hernias seen in the newborn period, with 80-90% occurring on the left side. The Morgagni hernia accounts for 2-6% of congenital diaphragmatic defects. The size of the defect is highly variable, ranging from a small hole to complete agenesis of this area of the diaphragm.

**CONGENITAL DIAPHRAGMATIC HERNIA (BOCHDALEK)**

**Pathology and Etiology**

Although CDH is characterized by a structural diaphragmatic defect, a major limiting factor for survival is the associated pulmonary hypoplasia. Lung hypoplasia was initially thought to be solely caused by the compression of the lung from the herniated abdominal contents, which impaired lung growth. However, emerging evidence indicates that pulmonary hypoplasia, at least in some cases, may precede the development of the diaphragmatic defect.

Pulmonary hypoplasia is characterized by a reduction in pulmonary mass and the number of bronchial divisions, respiratory bronchioles, and alveoli. The pathology of pulmonary hypoplasia and CDH includes abnormal septa in the terminal sacculles, thickened alveoli, and thickened pulmonary arterioles. Biochemical abnormalities include relative surfactant deficiencies, increased glycogen in the alveoli, and decreased levels of phosphatidylcholine, total DNA, and total lung protein, all of which contribute to limited gas exchange.

**Epidemiology**

The incidence of CDH is between 1/2,000 and 1/5,000 live births, with females affected twice as often as males. Defects are more common on the left (85%) and are occasionally (<5%) bilateral. Pulmonary hypoplasia and malrotation of the intestine are part of the lesion, not associated anomalies. Most cases of CDH are sporadic; familial cases have been reported. Associated anomalies have been reported in up to 30% of cases; these include CNS lesions, esophageal atresia, omphalocele, and cardiovascular lesions. CDH is recognized as part of several chromosomal syndromes: trisomy 21, trisomy 13, trisomy 18, Fryns, Brachmann-de Lange, Pallister-Killian, and Turner.

**Diagnosis and Clinical Presentation**

CDH can be diagnosed on prenatal ultrasonography (between 16 and 24 wk of gestation) in >50% of cases. High-speed fetal MRI can further define the lesion. Findings on ultrasonography may include polyhydramnios, chest mass, mediastinal shift, gastric bubble or a liver in the thoracic cavity, and fetal hydrops. Certain imaging features may predict outcome; these include lung:head size ratio. Nonetheless, no definitive characteristic reliably predicts outcome. After delivery, a chest radiograph is needed to confirm the diagnosis (Fig. 101-11). In some infants with an echogenic chest mass, further imaging is required. The differential diagnosis may include other diaphragm disorders such as eventration, a cystic lung lesion (pulmonary sequestration, cystic adenomatoid malformation), and others.

Arriving at the diagnosis early in pregnancy allows for prenatal counseling, possible fetal interventions, and planning for postnatal care. A referral to a center providing high-risk obstetrics, pediatric surgery, and tertiary care neonatology is advised. Careful evaluation for other anomalies should include echocardiography and amniocentesis. To avoid unnecessary pregnancy termination and unrealistic expectations, an experienced multidisciplinary group must carefully counsel the parents of a child diagnosed with a diaphragmatic hernia.

Respiratory distress is a cardinal sign in babies with CDH. It may occur immediately after birth or there may be a “honeymoon” period of up to 48 hr during which the baby is relatively stable. Early respiratory distress, within 6 hr after birth, is thought to be a poor prognostic sign. Respiratory distress is characterized clinically by tachypnea, grunt ing, use of accessory muscles, and cyanosis. *Children with CDH may also have a scaphoid abdomen and increased chest wall diameter.* Bowel sounds may also be heard in the chest with decreased breath sounds bilaterally. The point of maximal cardiac impulse may be displaced away from the side of the hernia if mediastinal shift has occurred. A chest x-ray and passage of a nasal gastric tube are all that is usually required to confirm the diagnosis.

A small group of infants with CDH present beyond the neonatal period. Patients with a delayed presentation may experience vomiting
Bibliography


as a result of intestinal obstruction or mild respiratory symptoms. Occasionally, incarceration of the intestine proceeds to ischemia with sepsis and shock. Unrecognized diaphragmatic hernia is a rare cause of sudden death in infants and toddlers. Group B streptococcal sepsis is a common cause of sudden death in newborns. The diagnosis is often delayed because of the atypical presentation.

**Treatment**

**Initial Management**

Aggressive respiratory support is often needed in children with CDH. This includes rapid endotracheal intubation, sedation, and possibly paralysis. Arterial (percutaneous and postductal) and central venous (umbilical) lines are mandated, as are a urinary catheter and nasogastric tube. A percutaneous arterial oxygen saturation (SpO₂) value of 95% should be the minimum goal. Prolonged mask ventilation in the delivery room, which enlarges the stomach and small bowel and thus reduces oxygenation, must be avoided. Volutrauma is a significant problem. Gentle ventilation with permissive hypercapnia reduces lung injury, need for ECMO, and mortality. Factors that contribute to pulmonary hypertension (hypoxia, acidosis, hypothermia) should be avoided. Echocardiography is important to guide therapeutic decisions by measuring pulmonary and systemic vascular pressures and defining the presence of cardiac dysfunction. Routine use of inotropes is indicated in the presence of left ventricular dysfunction. Babies with CDH may be surfactant deficient. Although surfactant is commonly used, no study has proven that it is beneficial in treatment of CDH.

**Ventilation Strategies**

Conventional mechanical ventilation, HFOV, and ECMO are the 3 main strategies to support respiratory failure in the newborn with CDH. The goal is to maintain oxygenation and carbon dioxide elimination without inducing volutrauma. The first modality to be used is conventional ventilation. Hyperventilation to induce alkalosis and decrease respiratory symptoms is not recommended. The ideal time to repair the diaphragmatic defect is under debate. Most experts wait at least 48 h after stabilization and resolution of pulmonary hypertension. Good relative indicators of stability are the requirement for conventional ventilation only, a low peak inspiratory pressure, and a FiO₂ < 0.5. If the newborn is on ECMO, an ability to wean from this support should be considered before surgical repair. In some centers, the repair is done with the cannulas in place; in other centers, the cannulas are removed. A subcostal approach is the most frequently used.

**Extracorporeal Membrane Oxygenation**

The availability of ECMO and the utility of preoperative stabilization have improved survival of babies with CDH. ECMO is the therapeutic option in children in whom conventional ventilation or conventional ventilation and HFOV fail. ECMO is most commonly used before repair of the defect. Several objective criteria for ECMO have been developed (see Chapter 101.7).

Birthweight and the 5-min Apgar score may be the best predictors of outcome in patients treated with ECMO. The lower limit of weight for ECMO is 2,000 g.

The duration of ECMO for neonates with diaphragmatic hernia is longer (7-14 days) than for those with persistent fetal circulation or meconium aspiration, and may last up to 2-4 wk. Timing of repair of the diaphragm while the infant receives ECMO is controversial; some experts prefer early repair to allow a greater duration of ECMO after the repair, whereas many defer repair until the infant has demonstrated the ability to tolerate weaning from ECMO. The recurrence of pulmonary hypertension is associated with a high mortality, and weaning from ECMO support should be cautious. If the patient cannot be weaned from ECMO after repair of CDH, options include discontinuing support and, in rare cases, lung transplantation.

**Novel Strategies for Infants with Congenital Diaphragmatic Hernia**

The most reliable prenatal prognosticators of outcomes in children with CDH studied is fetal ultrasonography. A prospective study using this modality at 24-26 wk compared fetal lung/head size ratio. There were no survivors when the lung/head size ratio was <1, and all babies with lung:head size ratio >1.4 survived. A second important consideration was the presence of liver in the thoracic cavity, which is a poor prognostic feature. Human studies have shown no benefit for in utero repair of CDH.

Tracheal occlusion in utero is based on the observation that in utero fetal lung fluid plays a critical role in lung growth and maturity. A deficiency of lung fluid results in pulmonary hypoplasia. Initial studies in affected fetuses have not demonstrated success, but new preliminary reports are showing some efficacy. Partial liquid ventilation after birth is an experimental therapy under investigation in adults and children with severe respiratory failure. Partial liquid ventilation increases FRC by recruiting collapsed alveoli, thereby improving ventilation-perfusion mismatches and compliance. It also may reduce lung injury and increase surfactant production.

**Surgical Repair**

The ideal time to repair the diaphragmatic defect is under debate. Most experts wait at least 48 h after stabilization and resolution of the pulmonary hypertension. Good relative indicators of stability are the requirement for conventional ventilation only, a low peak inspiratory pressure, and a FiO₂ < 50. If the newborn is on ECMO, an ability to wean from this support should be considered before surgical repair. In some centers, the repair is done with the cannulas in place; in other centers, the cannulas are removed. A subcostal approach is the most frequently used (Fig. 101-12). This allows for good visualization of the defect and, if the abdominal cavity cannot accommodate the herniated contents, a polymeric silicone (Silastic) patch can be placed. Both laparoscopic and thoracoscopic repairs have been reported, but these should be reserved for only the most stable infants.

The defect size and amount of native diaphragm present are variable. Whenever possible, a primary repair using native tissue is performed. If the defect is too large, a porous polytetrafluoroethylene (Gore-Tex) patch is used.
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The energy required to breathe. Many children normalize and “catch up” in growth by the time they are 2 yr old.

Neurocognitive defects are common and may result from the disease or the interventions. The incidence of neurologic abnormalities is higher in infants who require ECMO (67% vs. 24% of those who do not). The abnormalities are similar to those seen in neonates treated with ECMO for other diagnoses and include transient and permanent developmental delay, abnormal hearing or vision, and seizures. Serious hearing loss may occur in up to 28% of children who underwent ECMO. The majority of neurologic abnormalities are classified as mild to moderate.

Other long-term problems occurring in this population include pectus excavatum and scoliosis. Survivors of CDH repair, particularly those requiring ECMO support, have a variety of long-term abnormalities that appear to improve with time but require close monitoring and multidisciplinary support.

Bibliography is available at Expert Consult.

101.9 Foramen of Morgagni Hernia

Akhil Maheshwari and Waldemar A. Carlo

The anteromedial diaphragmatic defect through the foramen of Morgagni accounts for 2-6% of diaphragmatic hernias. Failure of the sternal and crural portions of the diaphragm to meet and fuse produces this defect. These defects are usually small, with a greater transverse than anteroposterior diameter, and are more commonly right-sided (90%) but may be bilateral (Fig. 101-13). The transverse colon or small intestine or liver is usually contained in the hernial sac. The majority of children with these defects are asymptomatic and are diagnosed beyond the neonatal period. The diagnosis is usually made on chest radiograph when a child is evaluated for another reason. The anteroposterior radiograph shows a structure behind the heart, and a lateral film localizes the mass to the retrosternal area. Chest CT or MRI will confirm the diagnosis. When symptoms occur, they can be recurrent respiratory infections, cough, vomiting, or reflux; in rare instances, incarceration may occur. Repair is recommended for all patients, in view of the risk of bowel strangulation, and can be accomplished laparoscopically or by an open approach. Prosthetic material is rarely required.
Bibliography
101.10 Paraesophageal Hernia
Akhil Maheshwari and Waldemar A. Carlo

Paraesophageal hernia is differentiated from hiatal hernia in that the gastroesophageal junction is in the normal location. The herniation of the stomach alongside or adjacent to the gastroesophageal junction is prone to incarceration with strangulation and perforation. A previous Nissen fundoplication and other diaphragmatic procedures are risk factors. This unusual diaphragmatic hernia should be repaired promptly after identification.

101.11 Eventration
Akhil Maheshwari and Waldemar A. Carlo

Eventration of the diaphragm is an abnormal elevation, consisting of a thinned diaphragmatic muscle that causes elevation of the entire hemidiaphragm or, more commonly, the anterior aspect of the hemidiaphragm. This elevation produces a paradoxical motion of the affected hemidiaphragm. Most eventrations are asymptomatic and do not require repair. A congenital form is the result of either incomplete development of the muscular portion or central tendon or abnormal development of the phrenic nerves. Congenital eventration may affect lung development, but it has not been associated with pulmonary hypoplasia. The differential diagnosis includes diaphragmatic paralysis, diaphragmatic hernia, traction injury, and iatrogenic injury after heart surgery. Eventration is also associated with pulmonary sequestration, congenital heart disease, and chromosomal trisomies. Most eventrations are asymptomatic and do not require repair. The indications for surgery include continued need for mechanical ventilation, recurrent infections, and failure to thrive. Large or symptomatic eventrations can be repaired by plication through an abdominal or thoracic approach that is minimally invasive.

Bibliography is available at Expert Consult.

101.12 Extrapulmonary Air Leaks (Pneumothorax, Pneumomediastinum, Pulmonary Interstitial Emphysema, Pneumopericardium)
Waldemar A. Carlo

Asymptomatic pneumothorax, usually unilateral, is estimated to occur in 1-2% of all newborn infants; symptomatic pneumothorax and pneumomediastinum are less common (see Chapter 94). The incidence of pneumothorax is increased in infants with lung diseases such as meconium aspiration and RDS; in those who receive assisted ventilation, especially if high ventilator support is necessary; and in infants with urinary tract anomalies or oligohydramnios.

ETIOLOGY AND PATHOPHYSIOLOGY
The most common cause of pneumothorax is overinflation resulting in alveolar rupture. It may be “spontaneous” or caused by underlying pulmonary disease, such as lobar emphysema or rupture of a congenital lung cyst or pneumatocele, to trauma, or to a “ball-valve” type of bronchial or bronchiolar obstruction resulting from aspiration. Pneumothorax associated with pulmonary hypoplasia is common, tends to occur during the 1st few hr after birth, and is caused by reduced alveolar surface area and poorly compliant lungs. It is associated with disorders of decreased amniotic fluid volume (Potter syndrome, renal agenesis, renal dysplasia, chronic amniotic fluid leak), decreased fetal breathing movement (oligohydramnios, neuromuscular disease), pulmonary space-occupying lesions (diaphragmatic hernia, pleural effusion, chylothorax), and thoracic abnormalities (thoracic dystrophies).

Gas from a ruptured alveolus escapes into the interstitial spaces of the lung, where it may cause interstitial emphysema or dissect along the peribronchial and perivascular connective tissue sheaths to the hilum of the lung. If the volume of escaped air is great enough, it may collect in the mediastinal space (pneumomediastinum) or rupture into the pleural space (pneumothorax), subcutaneous tissue (subcutaneous emphysema), peritoneal cavity (pneumoperitoneum), and/or pericardial sac (pneumopericardium). Rarely, increased mediastinal pressure may compress the pulmonary veins at the hilum and thereby interfere with pulmonary venous return to the heart and cardiac output. On occasion, air may embolize into the circulation (pulmonary air embolism) and produce cutaneous blanching, air in intravascular catheters, an air-filled heart and vessels on chest roentgenograms, and death.

Tension pneumothorax occurs if an accumulation of air within the pleural space is sufficient to elevate intrapleural pressure above atmospheric pressure. Unilateral tension pneumothorax results in impaired ventilation not only in the ipsilateral lung but also in the contralateral lung owing to a shift in the mediastinum toward the contralateral side. Compression of the vena cava and torsion of the great vessels may interfere with venous return.

CLINICAL MANIFESTATIONS
The physical findings of a clinically asymptomatic pneumothorax are hyperresonance and diminished breath sounds over the involved side of the chest with or without tachypnea.

Symptomatic pneumothorax is characterized by respiratory distress, which varies from merely high respiratory rate to severe dyspnea, tachypnea, and cyanosis. Irritability and restlessness or apnea may be the earliest signs. The onset is usually sudden but may be gradual; an infant may rapidly become critically ill. The chest may appear asymmetric with an increased anteroposterior diameter and bulging of the intercostal spaces on the affected side; other signs may be hyperresonance and diminished or absence of breath sounds. The heart is displaced toward the unaffected side, resulting in displacement of the cardiac apex and point of maximal impulse of the heart. The diaphragm is displaced downward, as is the liver with right-sided pneumothorax, and may result in abdominal distention. Because pneumothorax may be bilateral in approximately 10% of patients, symmetry of findings does not rule it out. In tension pneumothorax, signs of shock may be noted.

Pneumomediastinum can occur in patients with pneumothorax and is usually asymptomatic. The degree of respiratory distress depends on the amount of trapped gas. If it is great, bulging of the midthoracic area is observed, the neck veins are distended, and blood pressure is low. The last 2 findings are a result of tamponade of the systemic and pulmonary veins. Although often asymptomatic, subcutaneous emphysema in newborn infants is almost pathognomonic of pneumomediastinum.

Pulmonary interstitial emphysema may precede the development of a pneumothorax or may occur independently and lead to increasing respiratory distress as a result of decreased compliance, hypercapnia, and hypoxemia. Hypoxemia is caused by an increased alveolar–arterial oxygen gradient and intrapulmonary shunting. Progressive enlargement of blebs of gas may result in cystic dilation and respiratory deterioration resembling pneumothorax. In severe cases, pulmonary interstitial emphysema precedes the development of BPD. Avoidance of high inspiratory or mean airway pressures may prevent the development of pulmonary interstitial emphysema. Treatment may include bronchoscopy in patients with evidence of mucous plugging, selective intubation and ventilation of the uninvolved bronchus, oxygen, general respiratory care, and HPV.

DIAGNOSIS
Pneumothorax and other air leaks should be suspected in newborn infants who show signs of respiratory distress, are restless or irritable, or have a sudden change in condition. The diagnosis of pneumothorax is established by radiography, with the edge of the collapsed
Bibliography


Pneumopericardium may be asymptomatic, requiring only general supportive treatment, but it usually manifests as sudden shock with tachycardia, muffled heart sounds, and poor pulses suggesting tamponade. Pneumoperitoneum from air dissecting through the diaphragmatic apertures during mechanical ventilation may be confused with intestinal perforation. Abdominal paracentesis can be helpful in differentiating the two conditions. The presence of organisms on Gram stain of intestinal contents suggests the latter. Occasionally, pneumoperitoneum can result in an abdominal compartment syndrome requiring decompression.

Pneumomediastinum in a newborn infant. The anteroposterior view (left) demonstrates compression of the lungs, and the lateral view (right) shows bulging of the sternum, each resulting from distention of the mediastinum by trapped air.

Figure 101-14 A, Right-sided tension pneumothorax and widespread right lung pulmonary interstitial emphysema in a preterm infant receiving intensive care. B, Resolution of pneumothorax with a chest tube in place. Pulmonary interstitial emphysema (PIE) persists. (From Meerstadt PWD, Gyll C: Manual of neonatal emergency x-ray interpretation, Philadelphia, 1994, WB Saunders, p. 73.)
**TREATMENT**

Without a continued air leak, asymptomatic and mildly symptomatic small pneumothoraces require only close observation. Conservative management of a pneumothorax is effective even in selected infants requiring ventilatory support. Frequent small feedings may prevent gastric dilation and minimize crying, which can further compromise ventilation and worsen the pneumothorax. Breathing 100% oxygen in term infants may accelerate the resorption of free pleural air into blood by reducing the nitrogen tension in blood and producing a resultant nitrogen pressure gradient from the trapped gas in the blood, but the clinical effectiveness is not proven and the benefit must be weighed against the risks of oxygen toxicity. With severe respiratory or circulatory embarrassment, emergency aspiration using a soft small catheter introduced with a needle is indicated. Either immediately or after catheter aspiration, a chest tube should be inserted and attached to underwater seal drainage (see Fig. 101-14). If the air leak is ongoing, continuous suction (−5 to −20 cm H₂O) may be needed to evacuate the pneumothorax completely. A pneumopericardium requires prompt evacuation of entrapped air. Severe localized interstitial emphysema may respond to selective bronchial intubation. Judicious use of sedation in an infant fighting a ventilator may reduce the risk of pneumothorax. Surfactant therapy for RDS reduces the incidence of pneumothorax.

**Bibliography is available at Expert Consult.**

### 101.13 Pulmonary Hemorrhage

**Namasivayam Ambalavanan and Waldemar A. Carlo**

Massive pulmonary hemorrhage is a relatively uncommon, but catastrophic complication with a high risk of morbidity and mortality. Some degree of pulmonary hemorrhage occurs in about 10% of extremely preterm infants. However, massive pulmonary hemorrhage is less common and can be fatal. Autopsy demonstrates massive pulmonary hemorrhage in 15% of neonates who die in the 1st 2 wk of life. The reported incidence at autopsy varies from 1 to 4/1,000 live births. Approximately 75% of affected patients weigh <2,500 g at birth. Prophylactic indomethacin in extremely low birthweight infants reduces the incidence of pulmonary hemorrhage.

Most infants with pulmonary hemorrhage have had symptoms of respiratory distress that are indistinguishable from those of RDS. The onset may occur at birth or may be delayed several days. Hemorrhagic pulmonary edema is the source of blood in many cases and is associated with significant ductal shunting and high pulmonary blood flow or severe left-sided heart failure resulting from hypoxia. In severe cases, sudden cardiovascular collapse, poor lung compliance, profound cyanosis, and hypercapnia may be present. Radiographic findings are varied and nonspecific, ranging from minor streaking or patchy infiltrates to massive consolidation.

The incidence of pulmonary hemorrhage is increased in association with acute pulmonary infection, severe asphyxia, RDS, assisted ventilation, PDA, congenital heart disease, erythroblastosis fetalis, hemorrhagic disease of the newborn, thrombocytopenia, inborn errors of ammonia metabolism, and cold injury. Pulmonary hemorrhage is the only severe complication whose rate is increased with surfactant treatment. Pulmonary hemorrhage is seen with all surfactants; the incidence ranges from 1-5% of treated infants and is higher with natural surfactant. Bleeding is predominantly alveolar in approximately 65% of cases and interstitial in the rest. Bleeding into other organs is observed at autopsy of severely ill neonates, suggesting the possibility of an additional bleeding diathesis such as disseminated intravascular coagulation.

**Treatment** of pulmonary hemorrhage includes blood replacement, suctioning to clear the airway, intratracheal administration of epinephrine, and, in some cases, HFV. Although surfactant treatment has been associated with the development of pulmonary hemorrhage, administration of exogenous surfactant after the bleeding has occurred can improve lung compliance, because the presence of intra-alveolar blood and protein can inactivate surfactant.

Acute pulmonary hemorrhage may rarely occur in previously healthy full-term infants. The cause is unknown. Pulmonary hemorrhage may manifest as hemoptysis or blood in the nasopharynx or airway with no evidence of upper respiratory or gastrointestinal bleeding. Patients present with acute, severe respiratory failure requiring mechanical ventilation. Chest radiographs usually demonstrate bilateral alveolar infiltrates. The condition usually responds to intensive supportive treatment (see Chapter 407).

**Bibliography is available at Expert Consult.**
**Bibliography**


Bibliography
VOMITING

Vomiting or, more often, regurgitation is a relatively frequent symptom during the neonatal period. In the 1st few hr after birth, infants may vomit mucus, occasionally blood streaked. This vomiting rarely persists after the first few feedings; it may be caused by irritation of the gastric mucosa by material swallowed during delivery. If vomiting is protracted, gastric lavage with physiologic saline solution may relieve it.

When vomiting occurs shortly after birth and is persistent, the possibilities of intestinal obstruction, metabolic disorders, and increased intracranial pressure must be considered. A history of maternal polyhydramnios suggests upper gastrointestinal (esophageal, duodenal, ileal) atresia. Bile-stained emesis suggests intestinal obstruction beyond the duodenum but may also be idiopathic. Abdominal radiographs (kidney-ureter-bladder and cross-table lateral views) should be performed in neonates with persistent emesis and in all infants with bile-stained emesis to detect air–fluid levels, distended bowel loops, characteristic patterns of obstruction (double bubble: duodenal atresia), and pneumoperitoneum (that may be a result of intestinal perforation). A contrast swallow roentgenogram with small bowel follow-through is indicated in the presence of bilious emesis.

Obstructive lesions of the digestive tract are the most frequent gastrointestinal anomalies (see Chapters 319, 329, 330, and 332). Vomiting (and drooling) from esophageal obstruction occurs before or with the first feeding. The diagnosis of esophageal atresia can be suspected if unusual drooling from the mouth is observed and if resistance is encountered during an attempt to pass a catheter into the stomach. The diagnosis should be made before the infant has trouble with oral feedings and aspiration pneumonia develops. Infantile achalasia (cardiospasm), a rare cause of vomiting in newborn infants, is demonstrable radiographically as obstruction at the cardiac end of the esophagus without organic stenosis. Regurgitation of feedings because of continuous relaxation of the esophageal–gastric sphincter, or chalasia, is a cause of vomiting. Keeping the infant in a semiupright position, thickening the feeding, or administering prokinetic drugs can control it.

Vomiting caused by obstruction of the small intestine usually begins on the 1st day of life and is frequent, persistent, usually nonprojectile, copious, and, unless the obstruction is above the ampulla of Vater, bile-stained; it is associated with abdominal distention, visible deep peristaltic waves, and reduction or absence of bowel movements. Malrotation with obstruction from midgut volvulus is an acute emergency that must be not only considered but also urgently evaluated by an upper gastrointestinal contrast radiographic series. Radiographs of the
abdomen show the distribution of air in the intestine, which may point to the anatomic location of an obstruction; malrotation can be identified only by contrast studies. Normally, air can be demonstrated by radiographs in the jejunum by 15-60 min, in the ileum by 2-3 hr, and in the colon by 3 hr after birth. Absence of rectal gas at 24 hr is abnormal. Persistent vomiting may occur with congenital diaphragmatic hernia. The vomiting associated with pyloric stenosis may begin any time after birth but may not assume its characteristic pattern before the 2nd-3rd wk. Vomiting with obstruction is a common early sign of Hirschsprung disease. Vomiting may occur with many other disturbances that do not obstruct the digestive tract, such as milk allergy, adrenal hyperplasia of the salt-losing variety, galactosemia, hyperammonemias, organic acidoses, increased intracranial pressure, septicemia, meningitis, and urinary tract infection. In many infants, it is simply regurgitation from overfeeding or from failure to permit the infant to eructate swallowed air. (See Chapter 323 for a discussion of gastric emptying and gastroesophageal reflux.)

**DIARRHEA**
See Chapters 340 and 341.

**CONSTIPATION**
More than 90% of full-term newborn infants pass meconium within the 1st 24 hr. The possibility of intestinal obstruction should be considered in any infant who does not pass meconium by 24-36 hr. Intestinal atresia, stricture, or stenosis; Hirschsprung disease; milk bolus obstruction; meconium ileus; or meconium plugs may manifest as constipation or, more often, obstipation. Approximately 20% of very-low birthweight (VLBW) infants do not pass meconium within the 1st 24 hr. Constipation not present from birth but appearing during the 1st mo of life may be a sign of short-segment congenital aganglionic megacolon, hypothyroidism, strictures after necrotizing enterocolitis (NEC), or anal stenosis. It must be kept in mind that infrequent bowel movements do not necessarily mean constipation. A breastfed infant usually has frequent bowel movements, whereas a formula-fed infant may have 1-2 movements a day or every other day.

**MECONIUM PLUGS**
Lower colonic or anorectal plugs (Fig. 102-1) with a lower-than-normal water content may cause intestinal obstruction. Rarely, a firm mass of meconium may form elsewhere in the intestine and cause intrauterine intestinal obstruction and meconium peritonitis unrelated to cystic fibrosis (CF). Anorectal plugs may also cause mucosal ulceration and intestinal perforation. Meconium plugs are associated with small left colon syndrome in infants of diabetic mothers and with CF, rectal aganglionosis, maternal opiate use, and magnesium sulfate therapy for preeclampsia. The plug may be evacuated by glycerin suppository or enema with the iodinated contrast medium Gastrografin (melglumine diatrizoate, a hyperosmolar, water-soluble, radiopaque solution containing 0.1% polysorbate 80 [Tween 80] and 37% organically bound iodine) usually induce passage of the plug, presumably because the high osmolality (1,900 mOsm/L) of the solution draws fluid rapidly into the intestinal lumen and loosens inspissated material. Such rapid loss of fluid into the bowel may result in acute dehydration and shock, so it is advisable to dilute the contrast material with an equal amount of water, correct any existing dehydration, and provide intravenous fluids during and for several hours after the procedure. After removal of a meconium plug, the infant should be observed closely for the possible presence of congenital aganglionic megacolon.

102.1 Meconium Ileus in Cystic Fibrosis
Akhil Maheshwari and Waldemar A. Carlo

Impaction of meconium causes intestinal obstructions and may be associated with CF. The absence of fetal pancreatic enzymes in CF limits normal digestive activities in the intestine, and meconium becomes viscid and mucilaginous. It clings to the intestinal wall and moves with difficulty. The inspissated and impacted meconium fills the intestinal canal but is most concentrated in the lower part of the ileum. Clinically, the pattern is that of congenital intestinal obstruction with or without intestinal perforation. Abdominal distention is prominent, and vomiting becomes persistent. Infrequently, 1 or more inspissated meconium stools may be passed shortly after birth.

Meconium ileus is primarily associated with CF transmembrane regulator (CFTR) mutations F508del, G542X, W1282X, R553X, and G551D. Patients with 2 copies of the F508del mutation have a 25% chance of presenting with meconium ileus. F508del plus any “other” CF mutation confers 17% chance, and 2 “other” CF mutations confer a 12% chance of meconium ileus. In addition, non-CFTR genetic “modifier” genes influence meconium ileus. In families that already have at least 1 child with CF complicated by meconium ileus, there is a 39% recurrence rate for meconium ileus in subsequent children, which is more than the rates expected with autosomal recessive inheritance. In a twin study, 82% of monozygotic twins showed concordance for meconium ileus, whereas only 22% of dizygotic and 24% of 2 affected siblings showed concordance.

The differential diagnosis involves other causes of intestinal obstruction, including intestinal pseudoobstruction and other causes of pancreatic insufficiency (see Chapter 349). A presumptive diagnosis can be made on the basis of a history of CF in a sibling, via palpation of doughy or cordlike masses of intestines through the abdominal wall, and from the radiographic appearance. In contrast to the generally evenly distended intestinal loops above an atresia, the loops may vary in width and are not as evenly filled with gas. At points of heaviest meconium concentration, the infiltrated gas may create a bubbly granular appearance (Figs. 102-2 and 102-3). It is technically difficult to perform a sweat test in a neonate. Genetic testing confirms the diagnosis of CF.

**Treatment** for meconium ileus is high Gastrografin enema as described previously for meconium plugs. If the procedure is unsuccessful or perforation of the bowel wall is suspected, a laparotomy is performed and the ileum is opened at the point of largest diameter of the impaction. Approximately 50% of these infants have associated intestinal atresia, stenosis, or volvulus that requires surgery. The inspissated meconium is removed by gentle and patient irrigation with warm isotonic sodium chloride or acetylcysteine (Mucomyst) solution through a catheter passed between the impaction and the bowel wall. Most infants with meconium ileus survive the neonatal period. If meconium ileus is associated with CF, the long-term prognosis depends on the severity of the underlying disease (see Chapter 403).
MECONIUM PERITONITIS
Perforation of the intestine may occur in utero or shortly after birth. Frequently, the intestinal perforation seals naturally with relatively little meconium leakage into the peritoneal cavity. In some cases, with long-standing perforation, meconium peritonitis is more pronounced. Perforations occur most often as a complication of meconium ileus in infants with CF but are occasionally the result of a meconium plug or in utero intestinal obstruction of another cause. Cases at the most severe end of the spectrum may be diagnosed on prenatal ultrasonography with fetal ascites, polyhydramnios, bowel dilation, intraabdominal calcifications, and hydrops fetalis. At the other end are cases in which an intestinal perforation may seal spontaneously with only a minor meconium leak, so the event may never be detected except when meconium becomes calcified and is later discovered on radiographs of the abdomen. Alternatively, the clinical picture may be dominated by the signs of intestinal obstruction (as in meconium ileus) or chemical peritonitis. Characteristic clinical findings include abdominal distention, vomiting, and absence of stools. Treatment consists primarily of elimination of the intestinal obstruction and drainage of the peritoneal cavity.

102.2 NECROTIZING ENTEROCOLITIS
Akhil Maheshwari and Waldemar A. Carlo

NEC is the most common life-threatening emergency of the gastrointestinal tract in the newborn period. The disease is characterized by various degrees of mucosal or transmural necrosis of the intestine. The cause of NEC remains unclear but is most likely multifactorial. The incidence of NEC is 1-5% of infants in neonatal ICUs. Both incidence and case fatality rates increase with decreasing birth weight and gestational age. Because very small, ill preterm infants are particularly susceptible to NEC, a rising incidence may reflect improved survival of this high-risk group of patients.

PATHOLOGY AND PATHOGENESIS
Many factors may contribute to the development of a pathologic finding of NEC including necrotic segment of intestine, gas accumulation in the submucosa of the bowel wall (pneumatosis intestinalis), and progression of the necrosis to perforation, peritonitis, sepsis, and death. The distal part of the ileum and the proximal segment of colon are involved most frequently; in fatal cases, gangrene may extend from the stomach to the rectum. Although NEC is a multifactorial disease primarily associated with intestinal immaturity, the concept of "risk factors" for NEC is controversial. The triad of intestinal ischemia (injury), enteral nutrition (metabolic substrate), and bacterial translocation has classically been linked to NEC. The greatest risk factor for NEC is prematurity. The disorder probably results from an interaction between loss of mucosal integrity due to a variety of factors (ischemia, infection, inflammation) and the host's response to that injury (circular, immunologic, inflammatory), leading to necrosis of the affected area. Coagulation necrosis is the characteristic histologic finding in intestinal specimens. Clustering of cases suggests a primary role for an infectious agent. Various bacterial and viral agents, including Escherichia coli, Klebsiella, Clostridium perfringens, Staphylococcus epidermidis, astrovirus, norovirus, and rotavirus, have been recovered from cultures. Nonetheless, in most situations, a pathogen is not identified. NEC rarely occurs before the initiation of enteral feeding and is much less common in infants fed human milk. Aggressive enteral feeding may predispose to the development of NEC.

Although nearly 90% of all cases of NEC occur in preterm infants, the disease can occur in full-term neonates. NEC in term infants is often a "secondary" disease, seen more frequently in infants with history of birth asphyxia, Down syndrome, congenital heart disease, rotavirus infections, and Hirschsprung disease.

CLINICAL MANIFESTATIONS
Infants with NEC have a variety of signs and symptoms and may have an insidious or sudden catastrophic onset (Table 102-1). The onset of NEC is usually in the 2nd or 3rd wk of life but can be as late as 3 mo in VLBW infants. Age of onset is inversely related to gestational age. The first signs of impending disease may be nonspecific, including lethargy and temperature instability, or related to gastrointestinal pathology, such as abdominal distention and gastric retention. In some
extremely low birthweight infants, NEC may develop following a red cell transfusion. Bloody stools are seen in 25% of patients. Because of nonspecific signs, sepsis may be suspected before NEC. The spectrum of illness is broad, ranging from mild disease with only guaiac-positive stools to severe illness with bowel perforation, peritonitis, systemic inflammatory response syndrome, shock, and death. Progression may be rapid, but it is unusual for the disease to progress from mild to severe after 72 hr.

**DIAGNOSIS**

A very high index of suspicion in treating preterm at-risk infants is crucial. Plain abdominal radiographs are essential to make a diagnosis of NEC. The finding of pneumatosis intestinalis (air in the bowel wall) confirms the clinical suspicion of NEC and is diagnostic; 50-75% of patients have pneumatosis when treatment is started (Fig. 102-4). Portal venous gas is a sign of severe disease, and pneumoperitoneum indicates a perforation (Figs. 102-4 and 102-5). Hepatic sonography may detect portal venous gas in some infants with normal abdominal x-rays. The differential diagnosis of NEC includes specific infections (systemic or intestinal), gastrointestinal obstruction, volvulus, and isolated intestinal perforation. Idiopathic focal intestinal perforation can occur spontaneously or after the early use of postnatal steroids and indomethacin. Pneumoperitoneum develops in such patients, but they are usually less ill than those with NEC.

**TREATMENT**

Rapid initiation of therapy is required for suspected as well as proven cases of NEC. There is no definitive treatment for established NEC, so therapy is directed at giving supportive care and preventing further injury with cessation of feeding, nasogastric decompression, and administration of intravenous fluids. Careful attention to respiratory status, coagulation profile, and acid–base and electrolyte balances are important. Once blood has been drawn for culture, systemic antibiotics (with broad coverage based on the antibiotic sensitivity patterns of the gram-positive, Gram-negative, and anaerobic organisms in the particular neonatal ICU) should be started immediately. If present, umbilical catheters should be removed, but good intravenous access needs to be maintained. Ventilation should be assisted in the presence of apnea or if abdominal distension is contributing to hypoxia and hypercapnia. Intravascular volume replacement with crystalloid or blood products, cardiovascular support with fluid boluses and/or inotropes, and correction of hematologic, metabolic, and electrolyte abnormalities are essential to stabilize the infant with NEC.

The patient’s course should be monitored closely by means of frequent physical assessments; sequential anteroposterior and cross-table lateral or lateral decubitus abdominal radiographs to detect intestinal perforation; and serial determinations of hematologic, electrolyte, and acid–base status. Gown and glove isolation and grouping of infants at similar increased risks into cohorts separate from other infants should be instituted to contain an epidemic.

A surgeon should be consulted early in the course of treatment. **Indications for surgery** include evidence of perforation on abdominal x-ray (pneumoperitoneum) or positive result of abdominal paracentesis (stool or organism on Gram stain preparation from peritoneal fluid). Failure of medical management, a single fixed bowel loop on radiographs, abdominal wall erythema, and a palpable mass are relative indications for exploratory laparotomy. Ideally, surgery should be performed after intestinal necrosis develops but before perforation and peritonitis occur. In unstable premature infants with perforated NEC, **peritoneal drainage** can be cautiously considered as an alternative to exploratory laparotomy, although the best surgical approach in these infants remains unresolved. The type of surgical operation did not

| Table 102-1: Signs and Symptoms Associated with Necrotizing Enterocolitis |
|-----------------------------|-----------------------------|
| **GASTROINTESTINAL**        | Abdominal distention         |
|                             | Abdominal tenderness         |
|                             | Feeding intolerance          |
|                             | Delayed gastric emptying     |
|                             | Vomiting                     |
|                             | Occult/gross blood in stool  |
|                             | Change in stool pattern/diarrhea |
|                             | Abdominal mass               |
|                             | Erythema of abdominal wall   |
| **SYSTEMIC**                | Lethargy                     |
|                             | Apnea/respiratory distress   |
|                             | Temperature instability      |
|                             | “Not right”                  |
|                             | Acidosis (metabolic and/or respiratory) |
|                             | Glucose instability          |
|                             | Poor perfusion/shock         |
|                             | Disseminated intravascular coagulopathy |
|                             | Positive results of blood cultures |


**Figure 102-4** NEC. A kidney-ureter-bladder film demonstrates abdominal distention, hepatic portal venous gas (arrow), and a bubbly appearance of pneumatosis intestinalis (arrowhead; right lower quadrant). The latter 2 signs are thought to be pathognomonic for neonatal NEC.

**Figure 102-5** Intestinal perforation. A cross-table abdominal roentgenogram in a patient with a neonatal NEC demonstrates marked distention and massive pneumoperitoneum as evidenced by the free air below the anterior abdominal wall.
influence survival or other clinically important early outcomes in one multicenter study, but another large randomized trial showed that a majority of infants who were initially treated with peritoneal drains required a delayed secondary laparotomy. There are also some concerns about the long-term outcome (death or neurodevelopmental outcome) for infants treated with peritoneal drainage.

Patients with isolated intestinal perforation (not related to NEC) tend to have a lower birthweight, are less likely to be receiving oral feeding, and are prone to perforation at an earlier postnatal age than are patients with perforation related to NEC. In many patients with isolated intestinal perforation treated by drainage, no further surgical procedure is needed; a small subgroup may require later surgery to repair an intestinal stricture or fistula.

**PROGNOSIS**

Medical management fails in approximately 20–40% of patients with pneumatosis intestinalis at diagnosis; of these, 10–30% die. Early postoperative complications include wound infection, dehiscence, and stomal problems (prolapse, necrosis). Later complications include intestinal strictures, which develop at the site of the necrotizing lesion in approximately 10% of surgically or medically managed patients. Resection of the obstructing stricture is curative. After massive intestinal resection, complications from postoperative NEC include short-bowel syndrome (malabsorption, growth failure, malnutrition), complications related to central venous catheters (sepsis, thrombosis), and cholestatic jaundice. Preterm infants with NEC who require surgical intervention or who have concomitant bacteremia are at increased risk for adverse growth and neurodevelopmental outcome.

**PREVENTION**

Newborns exclusively breastfed have a reduced risk of NEC. There have been concerns about early and aggressive increase in feeding volumes in raising the risk of NEC in VLBW infants, although a safe feeding regimen remains unknown. Gut stimulation protocols consisting of minimal enteral feeds followed by judicious volume advancement decreased the incidence of NEC in smaller study cohorts, but significant benefits were not detected in a meta-analysis of all randomized studies. In other studies, slow advancement or delayed introduction of enteral feedings did not protect against NEC. Emerging evidence indicates that the use of inhibitors of gastric acid secretion (H2-receptor blockers, proton pump inhibitors) or prolonged empirical antibiotics in early neonatal period is associated with increased risk of NEC. Prophylactic enteral antibiotics reduced the risk of NEC in a study but although concerns about adverse outcomes persist, particularly related to the development of resistant bacteria. Extensive data and meta-analyses show that probiotic preparations decrease the incidence of severe NEC (stage II or higher) and mortality in preterm infants but an FDA-approved preparation is not available.

_Bibliography is available at Expert Consult._

**102.3 Jaundice and Hyperbilirubinemia in the Newborn**

_Namasivayam Ambalavanan and Waldemar A. Carlo_

Hyperbilirubinemia is a common and, in most cases, benign problem in neonates. Jaundice is observed during the 1st wk after birth in approximately 60% of term infants and 80% of preterm infants. The yellow color usually results from the accumulation of unconjugated, nonpolar, lipid-soluble bilirubin pigment in the skin. This unconjugated bilirubin (designated indirect-acting by nature of the Van den Bergh reaction) is an end product of heme-protein catabolism from a series of enzymatic reactions by heme-oxygenase and biliverdin reduc-tase and nonenzymatic reducing agents in the reticuloendothelial cells. It may also be partly caused by deposition of pigment from conjugated bilirubin, the end product from indirect, unconjugated bilirubin that has undergone conjugation in the liver cell microsome by the enzyme uridine diphosphoglucuronic acid (UDP)–glucuronyl transferase to form the polar, water-soluble glucuronide of bilirubin (direct-reacting). Although bilirubin may have a physiologic role as an antioxidant, elevations of indirect, unconjugated bilirubin are potentially neurotoxic. Even though the conjugated form is not neurotoxic, direct hyperbilirubinemia indicates a potentially serious hepatic disorder or a systemic illness.

**ETIOLOGY**

During the neonatal period, metabolism of bilirubin is in transition from the fetal stage, during which the placenta is the principal route of elimination of the lipid-soluble, unconjugated bilirubin, to the adult stage, during which the water-soluble conjugated form is excreted from hepatic cells into the biliary system and gastrointestinal tract. Unconjugated hyperbilirubinemia may be caused or increased by any factor that (a) increases the load of bilirubin to be metabolized by the liver (hemolytic anemias, polycythemia, bruising or internal hemorrhage, shortened red blood cell life as a result of immaturity or transfusion of cells, increased enterohepatic circulation, infection); (b) damages or reduces the activity of the transferase enzyme or other related enzymes (genetic deficiency, hypoxia, infection, thyroid deficiency); (c) competes for or blocks the transferase enzyme (drugs and other substances requiring glucuronic acid conjugation); or (d) leads to an absence or decreased amounts of the enzyme or to reduction of bilirubin uptake by liver cells (genetic defect, and prematurity). Gene polymorphisms in the hepatic uridine diphosphogluconate-glucuronyltransferase isozyme 1A1 (UGT1A1) and the solute carrier organic anion transporter 1B1 (SLCO1B1) alone or in combination influence the incidence of neonatal hyperbilirubinemia. The toxic effects of elevated serum concentrations of unconjugated bilirubin are increased by factors that reduce the retention of bilirubin in the circulation (hypoalbuminemia, displacement of bilirubin from its binding sites on albumin by competitive binding of drugs such as sulfisoxazole and moxalactam, acidosis, and increased free fatty acid concentration secondary to hypoglycemia, starvation, or hypothermia). Neurotoxic effects are directly related not only to the permeability of the blood–brain barrier and nerve cell membranes but also to neuronal susceptibility to injury, all of which are adversely influenced by asphyxia, prematurity, hyperosmolality, and infection. Early and frequent feeding decreases, whereas breastfeeding and dehydration increase, serum levels of bilirubin. Delay in passage of meconium, which contains 1 mg bilirubin/dL, may contribute to jaundice by enterohepatic recirculation after deconjugation by intestinal glucuronidase (Fig. 102-6). Drugs such as oxytocin (in the mother) and chemicals used in the nursery such as phenolic detergents may also produce unconjugated hyperbilirubinemia. Table 102-2 lists the risk factors for unconjugated hyperbilirubinemia. Additional risk factors include polycythemia, infection, prematurity, and having a diabetic mother.

**CLINICAL MANIFESTATIONS**

Jaundice usually appears during the early neonatal period, depending on etiology. Jaundice usually becomes apparent in a cephalocaudal progression, starting on the face and progressing to the abdomen and then the feet, as serum levels increase. Dermal pressure may reveal the anatomic progression of jaundice (face, ≈ 5 mg/dL; mid-abdomen, ≈ 15 mg/dL; soles, ≈ 20 mg/dL), but clinical examination cannot be depended on to estimate serum levels. Jaundice to the midabdomen, signs or symptoms, high-risk factors that suggest nonphysiologic jaundice, or hemolysis must be evaluated further (see Tables 102-2 and 102-3). Noninvasive techniques for transcutaneous measurement of bilirubin that correlate with serum levels may be used to screen infants, but determination of serum bilirubin level is indicated in patients with elevated age-specific transcutaneous bilirubin measurement, progressing jaundice, or risk for either hemolysis or sepsis. Whereas jaundice from deposition of indirect bilirubin in the skin tends to appear bright yellow or orange, jaundice of the obstructive type (direct bilirubin) has a greenish or muddy yellow cast. Infants with severe hyperbilirubinemia may present with lethargy and poor feeding and, without
The neonatal production rate of bilirubin is 6-8 mg/kg/24 hr (in contrast to 3-4 mg/kg/24 hr in adults). Water-insoluble bilirubin is bound to albumin. At the plasma-hepatocyte interface, a liver membrane carrier (biltranlocase) transports bilirubin to a cytosolic binding protein (ligandin or Y protein, now known to be glutathione S-transferase), which prevents back-absorption to plasma. Bilirubin is converted to bilirubin monoglucuronide (BMG). Neonates excrete more BMG than adults do. In the fetus, conjugated lipid-insoluble BMG and bilirubin diglucuronide (BDG) must be deconjugated by tissue \( \beta \)-glucuronidases to facilitate placental transfer of lipid-soluble unconjugated bilirubin across the placental lipid membranes. After birth, intestinal or milk-containing glucuronidases contribute to the enterohepatic recirculation of bilirubin and possibly to the development of hyperbilirubinemia.

### Table 102-2
Risk Factors for Development of Severe Hyperbilirubinemia in Infants ≥35 Wk of Gestation (in Approximate Order of Importance)

<table>
<thead>
<tr>
<th>MAJOR RISK FACTORS</th>
<th>MINOR RISK FACTORS</th>
<th>DECREASED RISK (THESE FACTORS ARE ASSOCIATED WITH DECREASED RISK OF SIGNIFICANT JAUNDICE, LISTED IN ORDER OF DECREASING IMPORTANCE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predischarge TSB or TcB level in the high-risk zone (see Fig. 102-8)</td>
<td>Predischarge TSB or TcB level in the high intermediate-risk zone</td>
<td>TSB or TcB level in the low-risk zone (see Fig. 102-8)</td>
</tr>
<tr>
<td>Jaundice observed in the 1st 24 hr</td>
<td>Jaundice observed before discharge</td>
<td>Gestational age ≥41 wk</td>
</tr>
<tr>
<td>Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (glucose-6-phosphate dehydrogenase deficiency), elevated end-titl CO concentration</td>
<td>Previous sibling received phototherapy</td>
<td>Exclusive bottle-feeding</td>
</tr>
<tr>
<td>Gestational age 35-36 wk</td>
<td>Cephalohematoma or significant bruising</td>
<td>Black race</td>
</tr>
<tr>
<td>Previous sibling with jaundice</td>
<td>Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive</td>
<td>Discharge from hospital after 72 hr</td>
</tr>
<tr>
<td>Macrosomic infant of a diabetic mother</td>
<td>Male gender</td>
<td>*Race as defined by mother's description.</td>
</tr>
</tbody>
</table>

### Table 102-3
Laboratory Evaluation of the Jaundiced Infant ≥35 Wk of Gestation

<table>
<thead>
<tr>
<th>INDICATIONS</th>
<th>ASSESSMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice in 1st 24 hr</td>
<td>Measure TcB and/or TSB</td>
</tr>
<tr>
<td>Jaundice appears excessive for infant’s age</td>
<td>Measure TcB and/or TSB</td>
</tr>
<tr>
<td>Infant receiving phototherapy or TSB rising rapidly (i.e., crossing percentiles [see Fig. 102-8]) and unexplained by history and physical examination</td>
<td>Blood type and Coombs test, if not obtained with cord blood</td>
</tr>
<tr>
<td></td>
<td>Complete blood count and smear</td>
</tr>
<tr>
<td></td>
<td>Measure direct or conjugated bilirubin</td>
</tr>
<tr>
<td></td>
<td>It is an option to perform reticulocyte count, G6PD, and ETCOc, if available</td>
</tr>
<tr>
<td></td>
<td>Repeat TSB in 4-24 hr depending on infant’s age and TSB level</td>
</tr>
<tr>
<td>TSB concentration approaching exchange levels or not responding to phototherapy</td>
<td>Perform reticulocyte count, G6PD, albumin, ETCO if available</td>
</tr>
<tr>
<td>Elevated direct (or conjugated) bilirubin level</td>
<td>Do urinalysis and urine culture</td>
</tr>
<tr>
<td></td>
<td>Evaluate for sepsis if indicated by history and physical examination</td>
</tr>
<tr>
<td>Jaundice present at or beyond age 3 wk, or sick infant</td>
<td>Total and direct (or conjugated) bilirubin level</td>
</tr>
<tr>
<td></td>
<td>If direct bilirubin elevated, evaluate for causes of cholestasis</td>
</tr>
<tr>
<td></td>
<td>Check results of newborn thyroid and galactosemia screen, and evaluate infant for signs or symptoms of hypothyroidism</td>
</tr>
</tbody>
</table>

ETCOc, end tidal carbon monoxide concentration; G6PD, glucose-6-phosphate dehydrogenase; TcB, transcutaneous bilirubin; TSB, total serum bilirubin.

treatment, can progress to acute bilirubin encephalopathy (kernicterus) (see Chapter 102.4).

**DIFFERENTIAL DIAGNOSIS**

Jaundice, consisting of either indirect or direct bilirubin, that is present at birth or appears within the 1st 24 hr after birth requires immediate attention and may be due to erythroblastosis fetalis, concealed hemorrhage, sepsis, or congenital infections, including syphilis, cytomegalovirus, rubella, and toxoplasmosis. Hemolysis is suggested by a rapid rise in serum bilirubin concentration (>0.5 mg/dL/hr), anemia, pallor, reticulocytosis, hepatosplenomegaly, and a positive family history. An unusually high proportion of direct-reacting bilirubin may characterize jaundice in infants who have received intravenous transfusions for erythroblastosis fetalis. Jaundice that first appears on the 2nd or 3rd day is usually physiologic but may represent a more severe form. Familial nonhemolytic icterus (Crigler-Najjar syndrome) and early-onset breastfeeding jaundice are seen initially on the 2nd or 3rd day. Jaundice appearing after the 3rd day and within the 1st wk suggests bacterial sepsis or urinary tract infection; it may also be due to other infections, notably syphilis, toxoplasmosis, cytomegalovirus, and enterovirus. Jaundice secondary to extensive ecchymosis or blood extravasation may occur during the 1st day or later, especially in premature infants. Polycythemia may also lead to early jaundice.

There is a long differential diagnosis for jaundice first recognized after the 1st wk of life, including breast milk jaundice, septicemia, congenital atresia or paucity of the bile ducts, hepatitis, galactosemia, hypothyroidism, CF, and congenital hemolytic anemia crises related to red blood cell morphology and enzyme deficiencies (Fig. 102-7). The differential diagnosis for persistent jaundice during the 1st mo of life includes hyperalimentation-associated cholestasis, hepatitis, cytomegalic inclusion disease, syphilis, toxoplasmosis, familial nonhemolytic icterus, congenital atresia of the bile ducts, galactosemia, and inspissated bile syndrome following hemolytic disease of the newborn. Rarely, physiologic jaundice may be prolonged for several weeks, as in infants with hypothyroidism or pyloric stenosis.

Full-term, low-risk, asymptomatic infants with jaundice may be evaluated by monitoring of total serum bilirubin levels. Regardless of gestation or time of appearance of jaundice, patients with significant hyperbilirubinemia and those with symptoms or signs require a complete diagnostic evaluation, which includes determination of direct and indirect bilirubin fractions, hemoglobin, reticulocyte count, blood type, Coombs test, and examination of a peripheral blood smear. Indirect hyperbilirubinemia, reticulocytosis, and a smear with evidence of red blood cell destruction suggest hemolysis (see Table 102-3). In the absence of blood group incompatibility, nonimmunologically induced hemolysis should be considered. If the reticulocyte count, Coombs test result, and direct bilirubin value are normal, physiologic or pathologic indirect hyperbilirubinemia may be present (see Fig. 102-7). If direct hyperbilirubinemia is present, hepatitis, congenital bile duct disorders (biliary atresia, paucity of bile ducts, Byler disease), cholestasis, inborn errors of metabolism, CF, and sepsis are diagnostic possibilities.

**PHYSIOLOGIC JAUNDICE (ICTERUS NEONATORUM)**

Under normal circumstances, the level of indirect bilirubin in umbilical cord serum is 1-3 mg/dL and rises at a rate of <5 mg/dL/24 hr; thus, jaundice becomes visible on the 2nd or 3rd day, usually peaking

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**Figure 102-7 Schematic approach to the diagnosis of neonatal jaundice. G6PD, glucose-6-phosphate dehydrogenase; PK, pyruvate kinase. (From Oski FA: Differential diagnosis of jaundice. In Taeusch HW, Ballard RA, Avery MA, editors: Schaffer and Avery's diseases of the newborn, ed 6, Philadelphia, 1991, WB Saunders.)**
between the 2nd and 4th days at 5-6 mg/dL and decreasing to <2 mg/dL between the 5th and 7th days after birth. Jaundice associated with these changes is designated physiologic and is believed to be the result of increased bilirubin production from the breakdown of fetal red blood cells combined with transient limitation in the conjugation of bilirubin by the immature neonatal liver.

Overall, 6-7% of full-term infants have indirect bilirubin levels >13 mg/dL and less than 3% have levels >15 mg/dL. Risk factors for elevated indirect bilirubin include maternal age, race (Chinese, Japanese, Korean, and Native American), maternal diabetes, prematurity, drugs (vitamin K3, novobiocin), altitude, polycythemia, male sex, trisomy 21, cutaneous bruising, blood extravasation (cephalohematoma), oxytocin induction, breastfeeding, weight loss (dehydration or caloric deprivation), delayed bowel movement, and a family history of or a sibling who had physiologic jaundice (see Table 102-2). In infants without these variables, indirect bilirubin levels rarely rise above 12 mg/dL, whereas infants with several risk factors are more likely to have higher bilirubin levels. A combination of breastfeeding, variant-glucuronosyltransferase activity (1A1), and alterations of the organic anion transporter 2 gene increases the risk of hyperbilirubinemia. Predicting which neonates are at risk for exaggerated physiologic jaundice can be based on hour-specific bilirubin levels in the 1st 24-72 hr of life (Fig. 102-8). Transcutaneous measurements of bilirubin are linearly correlated with serum levels and can be used for screening. Indirect bilirubin levels in full-term infants decline to adult levels (1 mg/dL) by 10-14 days of life. Persistent indirect hyperbilirubinemia beyond 2 wk suggests hemolysis, hereditary glucuronyl transferase deficiency, breast milk jaundice, hypothyroidism, or intestinal obstruction. Jaundice associated with pyloric stenosis may be the result of caloric deprivation, relative deficiency of hepatic UDP-glucuronyl transferase, or an increase in the enterohepatic circulation of bilirubin from the ileus. In premature infants, the rise in serum bilirubin tends to be the same or somewhat slower but of longer duration than in term infants. Peak levels of 8-12 mg/dL are not usually reached until the 4th-7th day, and jaundice is infrequently observed after the 10th day, corresponding to the maturation of mechanisms for bilirubin metabolism and excretion.

The diagnosis of physiologic jaundice in term or preterm infants can be established only by excluding known causes of jaundice on the basis of the history, clinical findings, and laboratory data (Table 102-4). In general, a search to determine the cause of jaundice should be made if (1) it appears in the 1st 24-36 hr after birth, (2) serum bilirubin is rising at a rate faster than 5 mg/dL/24 hr, (3) serum bilirubin is >12 mg/dL in a full-term infant (especially in the absence of risk factors) or 10-14 mg/dL in a preterm infant, (4) jaundice persists after 10-14 days after birth, or (5) direct bilirubin fraction is >2 mg/dL at any time. Other factors suggesting a nonphysiologic cause of jaundice are family history of hemolytic disease, pallor, hepatomegaly, splenomegaly, failure of phototherapy to lower the bilirubin level, vomiting, lethargy, poor feeding, excessive weight loss, apnea, bradycardia, abnormal vital signs (including hypothermia), light-colored stools, dark urine positive for bilirubin, and signs of kernicterus (see Chapter 102.4).

**PATHOLOGIC HYPERBILIRUBINEMIA**

Jaundice and its underlying hyperbilirubinemia are considered pathologic if the time of appearance, duration, or pattern varies significantly from that of physiologic jaundice or if the course is compatible with physiologic jaundice but other reasons exist to suspect that the infant is at special risk for neurotoxicity. It may not be possible to determine the precise cause of an abnormal elevation of unconjugated bilirubin, but many infants with this finding have associated risk factors such as Asian race, prematurity, breastfeeding, and weight loss. Frequently, the terms exaggerated physiologic jaundice and hyperbilirubinemia of the newborn are used in infants whose primary problem is probably a deficiency or inactivity of bilirubin glucuronyl transferase (Gilbert syndrome) rather than an excessive load of bilirubin for excretion (see Table 102-2). The combination of glucose-6-phosphate dehydrogenase (G6PD) deficiency and a mutation of the promoter region of UDP-glucuronyl transferase-1 produces indirect hyperbilirubinemia in the absence of signs of hemolysis. Nonphysiologic hyperbilirubinemia may also be caused by mutations in the gene for bilirubin UDP-glucuronyl transferase.

The greatest risk associated with indirect hyperbilirubinemia is the development of bilirubin-induced neurologic dysfunction, which typically occurs with high indirect bilirubin levels (see Chapter 102.4). The development of kernicterus (bilirubin encephalopathy) depends on the level of indirect bilirubin, duration of exposure to bilirubin elevation, the cause of jaundice, and the infant's well-being. Neurologic injury including kernicterus may occur at lower bilirubin levels in preterm infants and in the presence of asphyxia, intraventricular hemorrhage, hemolysis, or drugs that displace bilirubin from albumin. The exact serum indirect bilirubin level that is harmful for VLBW infants is unclear.

**JAUNDICE ASSOCIATED WITH BREAST-FEEDING**

Significant elevation in unconjugated bilirubin (breast milk jaundice) develops in an estimated 2% of breastfed term infants after the 7th day, with maximal concentrations as high as 10-30 mg/dL reached during the 2nd-3rd wk. If breastfeeding is continued, the bilirubin gradually decreases but may persist for 3-10 wk at lower levels. If nursing is discontinued, the serum bilirubin level falls rapidly, reaching normal range within a few days. With resumption of breastfeeding, bilirubin seldom returns to previously high levels. Phototherapy may be of benefit (see Chapter 102.4). Although uncommon, kernicterus can occur in patients with breast milk jaundice. The etiology of breast milk jaundice is not entirely clear but may be attributed to the presence of glucuronidase in some breast milk.

The late jaundice associated with breastfeeding should be distinguished from an early-onset, accentuated unconjugated hyperbilirubinemia known as breastfeeding jaundice, which occurs in the 1st wk after birth in breastfed infants, who normally have higher bilirubin levels than formula-fed infants (Fig. 102-9). Hyperbilirubinemia (>12 mg/dL) develops in 13% of breastfed infants during the 1st wk and may be a result of decreased milk intake with dehydration and/or reduced caloric intake. Prophylactic supplements of glucose water to breastfed infants are associated with higher bilirubin levels, in part because of reduced intake of the higher–caloric density breast milk. Frequent breastfeeding (>10/24 hr), rooming-in with night feeding,
Table 102-4  Diagnostic Features of the Various Types of Neonatal Jaundice

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>NATURE OF VAN DEN BERGH REACTION</th>
<th>JAUNDICE</th>
<th>PEAK BILIRUBIN CONCENTRATION</th>
<th>BILIRUBIN RATE OF ACCUMULATION (mg/dL/day)</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Physiologic jaundice&quot;:</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Full-term</td>
<td>Indirect</td>
<td>Appears</td>
<td>2-3 days</td>
<td>10-12</td>
<td>2-3</td>
</tr>
<tr>
<td>Premature</td>
<td>Indirect</td>
<td>Disappears</td>
<td>4-5 days</td>
<td>15</td>
<td>6-8</td>
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<td></td>
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<tr>
<td>Hyperbilirubinemia caused by</td>
<td></td>
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<td></td>
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<tr>
<td>metabolic factors:</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Full-term</td>
<td>Indirect</td>
<td>Appears</td>
<td>2-3 days</td>
<td>&gt;12</td>
<td>1st wk</td>
</tr>
<tr>
<td>Premature</td>
<td>Indirect</td>
<td>Disappears</td>
<td>3-4 days</td>
<td>&gt;15</td>
<td>1st wk</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hemolytic states and hematoma</td>
<td>Indirect</td>
<td>May appear in 1st 24 hr</td>
<td>Variable</td>
<td>Unlimited</td>
<td>Variable</td>
</tr>
<tr>
<td>Mixed hemolytic and hepatotoxic</td>
<td>Indirect</td>
<td>May appear in 1st 24 hr</td>
<td>Variable</td>
<td>Unlimited</td>
<td>Variable</td>
</tr>
<tr>
<td>factors</td>
<td>Direct</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocellular damage</td>
<td>Indirect</td>
<td>Usually 2-3 days; may appear by 2nd wk</td>
<td>Variable</td>
<td>Unlimited</td>
<td>Variable</td>
</tr>
</tbody>
</table>


Figure 102-9  Distribution of maximal bilirubin levels during the 1st wk of life in breastfed and formula-fed white infants weighing more than 2,500 g. (From Maisels MJ, Gifford K: Normal serum bilirubin levels in the newborn and the effect of breast-feeding, Pediatrics 78:837–843, 1986.)

and ongoing lactation support may reduce the incidence of early breastfeeding jaundice. Even when breastfeeding jaundice develops, breastfeeding should be continued if possible. It is an option to temporar...
Bibliography


Kernicterus, or bilirubin encephalopathy, is a neurologic syndrome resulting from the deposition of unconjugated (indirect) bilirubin in the basal ganglia and brainstem nuclei. The pathogenesis of kernicterus is multifactorial and involves an interaction between unconjugated bilirubin levels, albumin binding and unbound bilirubin levels, passage across the blood-brain barrier, and neuronal susceptibility to injury. Disruption of the blood–brain barrier by disease, asphyxia, and other factors and maturational changes in blood–brain barrier permeability affect risk.

The precise blood level above which indirect-reacting bilirubin or free bilirubin will be toxic for an individual infant is unpredictable, but in a large series, kernicterus occurred only in infants with a bilirubin >20 mg/dL. Ninety percent of the infants in whom kernicterus developed were in previously healthy, predominantly breastfed term and near-term infants. The duration of exposure to high bilirubin levels needed to produce toxic effects are unknown. The more immature the infant is, the greater the susceptibility to kernicterus. Chapter 102.3 discusses the factors that potentiate the movement of bilirubin across the blood–brain barrier and into brain cells.

CLINICAL MANIFESTATIONS

Signs and symptoms of kernicterus usually appear 2-5 days after birth in term infants and as late as the 7th day in preterm infants, but hyperbilirubinemia may lead to encephalopathy at any time during the neonatal period. The early signs may be subtle and indistinguishable from those of sepsis, asphyxia, hypoglycemia, intracranial hemorrhage, and other acute systemic illnesses in a neonate. Lethargy, poor feeding, and loss of the Moro reflex are common initial signs. Subsequently, the infant may appear gravelly ill and prostrate, with diminished tendon reflexes and respiratory distress. Opisthotonos with a bulging fontanel, twitching of the face or limbs, and a shrill high-pitched cry may follow. In advanced cases, convulsions and spasm occur, with affected infants stiffly extending their arms in an inward rotation with the fists clenched (Table 102-5). Rrigidity is rare at this late stage.

Many infants who progress to these severe neurologic signs die; the survivors are usually seriously damaged but may appear to recover and for 2-3 mo show few abnormalities. Later in the 1st yr, opisthotonus, muscle rigidity, irregular movements, and convulsions tend to recur. In the 2nd yr, the opisthotonus and seizures abate, but irregular, involuntary movements, muscle rigidity, or, in some infants, hypotonia increase steadily. By 3 yr of age, the complete neurologic syndrome is often apparent; it consists of bilateral choreoathetosis with involuntary muscle spasms, extrapyramidal signs, seizures, mental deficiency, dystonic speech, high-frequency hearing loss, squinting, and defective upward eye movements. Pyramidal signs, hypotonia, and ataxia occur in a few infants. In mildly affected infants, the syndrome may be characterized only by mild to moderate neuromuscular incoordination, partial deafness, or “minimal brain dysfunction,” occurring singly or in combination; these problems may be unapparent until the child enters school (see Table 102-5).

INCIDENCE AND PROGNOSIS

By pathologic criteria, kernicterus develops in 30% of infants (all gestational ages) with untreated hemolytic disease and bilirubin levels >25-30 mg/dL. The incidence at autopsy in hyperbilirubinemic preterm infants is 2-16% and is related to the risk factors discussed in Chapter 102.3. Reliable estimates of the frequency of the clinical syndrome are not available because of the wide spectrum of manifestations. Overt neurologic signs have a grave prognosis; more than 75% of infants die, and 80% of affected survivors have bilateral choreoathetosis with involuntary muscle spasms. Mental retardation, deafness, and spastic quadriplegia are common.

PREVENTION

Although kernicterus has been thought to be a disease of the past, there are reports of neurotoxic effects of bilirubin in term and near-term infants who were discharged as healthy newborns. Experts recommend universal screening for hyperbilirubinemia in the 1st 24-48 hr after birth to detect infants at high risk for severe jaundice and bilirubin-induced neurologic dysfunction.

Effective prevention requires ongoing vigilance and a practical, system-based approach in order to distinguish infants with benign newborn jaundice from those whose course may be less predictable and potentially harmful. Protocols using the hour-specific bilirubin nomogram (see Fig. 102-8), physical examination, and clinical risk factors have been successful in identifying patients at risk for hyperbilirubinemia and candidates for targeted management. The American Academy of Pediatrics has identified potentially preventable causes of kernicterus, as follows: (1) early discharge (<48 hr) with no early follow-up (within 48 hr of discharge); this problem is particularly important in near-term infants (35-37 wk of gestation); (2) failure to check the bilirubin level in an infant noted to be jaundiced in the 1st 24 hr; (3) failure to recognize the presence of risk factors for hyperbilirubinemia; (4) understimation of the severity of jaundice by clinical (visual) assessment; (5) lack of concern regarding the presence of jaundice; (6) delay in measuring the serum bilirubin level despite marked jaundice or delay in initiating phototherapy in the presence of elevated bilirubin levels; and (7) failure to respond to parental concern regarding jaundice, poor feeding, or lethargy. Figure 102-10 is an evidence-based management algorithm for infants. In addition, it is recommended to determine before discharge each infant's risk factors from established protocols (see Table 102-2).

The following approach is further recommended: (1) any infant who is jaundiced before 24 hr requires measurement of total and direct serum bilirubin levels and, if it is elevated, evaluation for possible hemolytic disease and (2) follow-up should be provided within 2-3 days of discharge to all neonates discharged earlier than 48 hr after birth. Early follow-up is particularly important for infants younger than 38 wk of gestation. The timing of follow-up depends on the age at discharge and the presence of risk factors. In some cases, follow-up within 24 hr is necessary. Postdischarge follow-up is essential for early recognition of problems related to hyperbilirubinemia and disease progression. Parental communication with regard to concerns about infant's skin color and behavioral activities should be addressed early and frequently, including education about potential risks and neurotoxicity. Ongoing lactation promotion, education, support, and follow-up services are essential throughout the neonatal period. Mothers should be advised to nurse their infants every 2-3 hr and to avoid routine supplementation with water or glucose water in order to ensure adequate hydration and caloric intake.

TREATMENT OF HYPERBILIRUBINEMIA

Regardless of the cause, the goal of therapy is to prevent neurotoxicity related to indirect-reacting bilirubin while not causing undue harm. Phototherapy and, if it is unsuccessful, exchange transfusion remain the primary treatment modalities used to keep the maximal total serum bilirubin below pathologic levels (Figs. 102-11 and 102-12;
Clinical jaundice and indirect hyperbilirubinemia are reduced by exposure to a high intensity of light in the visible spectrum. Bilirubin absorbs light maximally in the blue range (420-470 nm). Broad-spectrum white, blue, and special narrow-spectrum (super) blue lights have been effective in reducing bilirubin levels. Bilirubin in the skin absorbs light energy, causing several photochemical reactions. One major product from phototherapy is a result of a reversible photosomerization reaction converting the toxic native unconjugated 4Z,15Z-bilirubin into an unconjugated configurational isomer, 4Z,15E-bilirubin, which can then be excreted in bile without conjugation. The other major product from phototherapy is lumirubin, which is an irreversible structural isomer converted from native bilirubin that can be excreted by the kidneys in the unconjugated state.

The therapeutic effect of phototherapy depends on the light energy emitted in the effective range of wavelengths, the distance between the lights and the infant, and the surface area of exposed skin, as well as the rate of hemolysis and in vivo metabolism and excretion of bilirubin. Available commercial phototherapy units vary considerably in spectral output and the intensity of radiance emitted; therefore, the wattage can be accurately measured only at the patient’s skin surface. Dark skin does not reduce the efficacy of phototherapy. Maximal intensive phototherapy should be used when indirect bilirubin levels approach those noted in Figure 102-11 and Table 102-7. Such therapy includes using “special blue” fluorescent tubes, placing the lamps within 15-20 cm of the infant, and putting a fiberoptic phototherapy blanket under the infant’s back to increase the exposed surface area. Aggressive phototherapy may improve neurodevelopmental outcome in infants <1,000 g.

The use of phototherapy has decreased the need for exchange transfusion in term and preterm infants with hemolytic and nonhemolytic jaundice. When indications for exchange transfusion are present, phototherapy should not be used as a substitute; however, phototherapy may reduce the need for repeated exchange transfusions in infants with hemolysis. Conventional phototherapy is applied continuously, and the infant is turned frequently for maximal skin surface area exposure. It should be discontinued as soon as the indirect bilirubin concentration has reduced to levels considered safe with respect to the infant’s age and condition. Serum bilirubin levels and hematocrit should be monitored every 4-8 hr in infants with hemolytic disease and those with bilirubin levels near toxic range for the individual infant. Others, particularly older neonate, may be monitored less frequently. Serum bilirubin monitoring should continue for at least 24 hr after cessation of phototherapy in patients with hemolytic disease, because unexpected rises in bilirubin may occur, requiring further treatment. Skin color cannot be relied on for evaluating the effectiveness of phototherapy; the skin of babies exposed to light may appear to be almost without jaundice in the presence of marked hyperbilirubinemia. Although not necessary for all affected infants, intravenous fluid supplementation added to oral feedings may be beneficial in dehydrated patients or infants with bilirubin levels nearing those requiring exchange transfusion.

Complications associated with phototherapy include loose stools, erythematous macular rash, purpuric rash associated with transient porphyrinemia, overheating, dehydration (increased insensible water loss, diarrhea), hypothermia from exposure, and a benign condition called bronze baby syndrome (which occurs in the presence of direct hyperbilirubinemia). Phototherapy is contraindicated in the presence of porphyria. Before phototherapy is initiated, the infant’s eyes should be closed and adequately covered to prevent light exposure and corneal damage. Body temperature should be monitored, and the infant should be shielded from bulb breakage. Irradiance should be measured directly. In infants with hemolytic disease, care must be taken to monitor for the development of anemia, which may require transfusion. Anemia may develop despite lowering of bilirubin levels. Clinical experience suggests that long-term adverse biologic effects of phototherapy are absent, minimal, or unrecognized.

The term bronze baby syndrome refers to a sometimes-noted dark, grayish brown skin discoloration in infants undergoing phototherapy. Almost all infants observed with this syndrome have had significant elevation of direct-reacting bilirubin and other evidence of obstructive liver disease. The discoloration may result from photo-induced modification of porphyrins, which are often present during cholestatic jaundice and may last for many months. Despite the bronze baby syndrome, phototherapy can continue if needed.

Intravenous Immunoglobulin
The administration of intravenous immunoglobulin is an adjunctive treatment for hyperbilirubinemia caused by isoimmune hemolytic disease. Its use is recommended when serum bilirubin is approaching exchange levels despite maximal interventions including phototherapy. Intravenous immunoglobulin (0.5-1.0 g/kg/dose; repeat in 12 hr) reduces the need for exchange transfusion in both ABO and Rh hemolytic disease, presumably by reducing hemolysis.

Metalloporphyrins
A potentially important alternative therapy is the use of metalloporphyrins for hyperbilirubinemia. The metalloporphyrin Sn-mesoporphyrin (SnMP) offers promise as a drug candidate. The proposed mechanism of action is competitive enzymatic inhibition of the rate-limiting conversion of heme-protein to biliverdin (an intermediate metabolite in the production of unconjugated bilirubin) by hemooxygenase. A single intramuscular dose on the 1st day of life may reduce the need for subsequent phototherapy. Such therapy may be beneficial when jaundice is anticipated, particularly in patients with ABO incompatibility or G6PD deficiency, or when blood products are objected to, as with Jehovah’s Witness patients. Complications from metalloporphyrins include transient erythema if the infant is receiving phototherapy. Administration of SnMP may reduce bilirubin levels and decrease both the need for phototherapy and the duration of hospital stay; however, it remains unclear whether treatment with metalloporphyrins for unconjugated hyperbilirubinemia will alter the risk of kernicterus or long-term neurodevelopment impairment. Data on efficacy, toxicity, and long-term benefit are currently being evaluated.

Exchange Transfusion
Double-volume exchange transfusion is performed if intensive phototherapy has failed to reduce bilirubin levels to a safe range and if the

<table>
<thead>
<tr>
<th>BIRTHWEIGHT (g)</th>
<th>UNCOMPLICATED*</th>
<th>COMPLICATED*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1,000</td>
<td>12-13</td>
<td>10-12</td>
</tr>
<tr>
<td>1,000-1,250</td>
<td>12-14</td>
<td>10-12</td>
</tr>
<tr>
<td>1,251-1,499</td>
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<tr>
<td>1,500-1,999</td>
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<td>15-17</td>
</tr>
<tr>
<td>2,000-2,500</td>
<td>20-22</td>
<td>18-20</td>
</tr>
</tbody>
</table>

*Complications include perinatal asphyxia, acidosis, hypoxia, hypothermia, hypoaalbuminemia, meningitis, intraventricular hemorrhage, hemolysis, hypoglycemia, or signs of kernicterus. Phototherapy is usually started at 50-70% of the maximal indirect level. If values greatly exceed this level, if phototherapy is unsuccessful in reducing the maximal bilirubin level, or if signs of kernicterus are evident, exchange transfusion is indicated.
risk of kernicterus exceeds the risk of the procedure. Potential complications from exchange transfusion are not trivial and include metabolic acidosis, electrolyte abnormalities, hypoglycemia, hypocalcemia, thrombocytopenia, volume overload, arrhythmias, NEC, infection, graft-versus-host disease, and death. This widely accepted treatment is repeated if necessary to keep indirect bilirubin levels in a safe range (see Fig. 102-12 and Table 102-7). See “Exchange Transfusion” in Chapter 103.

Various factors may influence the decision to perform a double-volume exchange transfusion in an individual patient. The appearance of clinical signs suggesting kernicterus is an indication for exchange transfusion at any level of serum bilirubin. A healthy full-term infant

risk of kernicterus exceeds the risk of the procedure. Potential complications from exchange transfusion are not trivial and include metabolic acidosis, electrolyte abnormalities, hypoglycemia, hypocalcemia, thrombocytopenia, volume overload, arrhythmias, NEC, infection, graft-versus-host disease, and death. This widely accepted treatment is repeated if necessary to keep indirect bilirubin levels in a safe range (see Fig. 102-12 and Table 102-7). See “Exchange Transfusion” in Chapter 103.

Various factors may influence the decision to perform a double-volume exchange transfusion in an individual patient. The appearance of clinical signs suggesting kernicterus is an indication for exchange transfusion at any level of serum bilirubin. A healthy full-term infant
• Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
• Risk factors — isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0 g/dL (if measured).
• For well infants 35-37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37 6/7 wk.
• It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50 mmol/L) below those shown, but home phototherapy should not be used in any infant with risk factors.

**Figure 102-11 Guidelines for phototherapy in hospitalized infants of ≥35 wk of gestation.** Note: These guidelines are based on limited evidence, and the levels shown are approximations. The guidelines refer to the use of intensive phototherapy, which should be used when the total serum bilirubin (TSB) exceeds the line indicated for each category. Infants are designated as “higher risk” because of the potential negative effects of the conditions listed on albumin binding of bilirubin, the blood–brain barrier, and the susceptibility of the brain cells to damage by bilirubin. “Intensive phototherapy” implies irradiance in the blue-green spectrum (wavelengths approximately 430-490 nm) of at least 30 µW/cm²/nm (measured at the infant’s skin directly below the center of the phototherapy unit) and delivered to as much of the infant’s skin surface area as possible. Note that irradiance measured below the center of the light source is much greater than that measured at the periphery. Measurements should be made with a radiometer specified by the manufacturer of the phototherapy system. If TSB levels approach or exceed the exchange transfusion line (see Fig. 102-12), the sides of the bassinette, incubator, or warmer should be lined with aluminum foil or white material, to increase both the surface area of the infant exposed and the efficacy of phototherapy. The presence of hemolysis is strongly suggested if the TSB does not decrease in the first 24 hr. The following B/A (bilirubin: albumin) ratios can be used together with, but not in lieu of, the TSB level as an additional factor in determining the need for exchange transfusion. G6PD, glucose-6-phosphate dehydrogenase. (From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation, Pediatrics 114:297–316, 2004.)

**Figure 102-12 Guidelines for exchange transfusion in hospitalized infants of ≥35 wk of gestation.** Note: These suggested levels represent a consensus of most of the committee but are based on limited evidence, and the levels shown are approximations. During birth hospitalization, exchange transfusion is recommended if the total serum bilirubin (TSB) rises to these levels despite intensive phototherapy. In a readmitted infant, if the TSB level is above the exchange level, TSB measurement should be repeated every 2-3 hr; exchange transfusion should be considered if the TSB remains above the levels indicated after intensive phototherapy for 6 hr. The following B:A (bilirubin: albumin) ratios can be used together with, but not in lieu of, the TSB level as an additional factor in determining the need for exchange transfusion. G6PD, glucose-6-phosphate dehydrogenase. (From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation, Pediatrics 114:297–316, 2004.)
Table 102-7  Example of a Clinical Pathway for Management of the Newborn Infant Readmitted for Phototherapy or Exchange Transfusion

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>Use intensive phototherapy and/or exchange transfusion as indicated in Figs. 102-11 and 102-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>LABORATORY TESTS</td>
<td>TSB and direct bilirubin levels Blood type (ABO, Rh) Direct antibody test (Coombs) Serum albumin Complete blood cell count with differential and smear for red cell morphology Reticulocyte count End-tidal CO concentration (if available) Glucose-6-phosphate dehydrogenase if suggested by ethnic or geographic origin or if poor response to phototherapy Urine for reducing substances If history and/or presentation suggest sepsis, perform blood culture, urine culture, and cerebrospinal fluid for protein, glucose, cell count, and culture</td>
</tr>
<tr>
<td>INTERVENTIONS</td>
<td>If TSB ≥25 mg/dL (428 µmol/L) or ≥20 mg/dL (342 µmol/L) in a sick infant or infant &lt;38 wk gestation, obtain a type and crossmatch, and request blood in case an exchange transfusion is necessary In infants with isoimmune hemolytic disease and TSB level rising in spite of intensive phototherapy or within 2-3 mg/dL (34-51 µmol/L) of exchange level (see Fig. 102-12), administer intravenous immunoglobulin 0.5-1 g/kg over 2 hr and repeat in 12 hr if necessary If infant’s weight loss from birth is &gt;12% or there is clinical or biochemical evidence of dehydration, recommend formula or expressed breast milk. If oral intake is in question, give intravenous fluids</td>
</tr>
<tr>
<td>FOR INFANTS RECEIVING INTENSIVE PHOTOTHERAPY:</td>
<td>Breastfeed or bottle-feed (formula or expressed breast milk) every 2-3 hr If TSB ≥25 mg/dL (428 µmol/L), repeat TSB within 2-3 hr If TSB 20-25 mg/dL (342-428 µmol/L), repeat within 3-4 hr. If TSB &lt;20 mg/dL (342 µmol/L), repeat in 4-6 hr. If TSB continues to fall, repeat in 8-12 hr If TSB is not decreasing or is moving closer to level for exchange transfusion or the TSB/albumin ratio exceeds levels shown in Fig. 102-12, consider exchange transfusion (see Fig. 102-12 for exchange transfusion recommendations) When TSB is &lt;13-14 mg/dL (239 µmol/L), discontinue phototherapy Depending on the cause of the hyperbilirubinemia, it is an option to measure TSB 24 hr after discharge to check for rebound</td>
</tr>
</tbody>
</table>

TSB, total serum bilirubin.


with physiologic or breast milk jaundice may tolerate a concentration slightly higher than 25 mg/dL with no apparent ill effect, whereas kernicterus may develop in a sick premature infant at a significantly lower level. A level approaching that considered critical for the individual infant may be an indication for exchange transfusion during the 1st or 2nd day after birth when a further rise is anticipated, but not typically after the 4th day in a term infant or after the 7th day in a premature infant because an imminent fall may be anticipated as the hepatic conjugating mechanism becomes more effective.

Bibliography is available at Expert Consult.
Chapter 102  •  Digestive System Disorders  880.e1

Bibliography
Blood Disorders
Akhil Maheshwari and Waldemar A. Carlo

103.1 Anemia in the Newborn Infant
Akhil Maheshwari and Waldemar A. Carlo

Hemoglobin increases with advancing gestational age; at term, cord blood hemoglobin is 16.8 g/dL (14-20 g/dL); hemoglobin levels in very-low birthweight (VLBW) infants are 1-2 g/dL below those in term infants (Fig. 103-1). A hemoglobin value less than the normal range of hemoglobin for birthweight and postnatal age is defined as anemia (Table 103-1). A "physiologic" decrease in hemoglobin content is noticed at 8-12 wk in term infants (hemoglobin, 11 g/dL) and at approximately 6 wk in premature infants (7-10 g/dL).

Infants born by cesarean section may have a lower hematocrit than those born vaginally. Anemia at birth manifests as pallor, heart failure, or shock (Fig. 103-2). It may be caused by acute or chronic fetal blood loss, hemolysis, or underproduction of erythrocytes. Specific causes include hemolytic disease of the newborn, tearing or cutting of the umbilical cord during delivery, abnormal cord insertion, communicating placental vessels, placenta previa or abruptio, nuchal cord, incision into the placenta, internal hemorrhage (liver, spleen, intracranial), α-thalassemia, congenital parvovirus infection or other hypoplastic anemias, and twin–twin transfusion in monozygotic twins with arteriovenous placental connections (see Chapter 98).

Transplacental hemorrhage with bleeding from the fetal into the maternal circulation has been reported in 5-15% of pregnancies, but, unless severe, it is not usually sufficient to cause clinically apparent anemia at birth. The cause of transplacental hemorrhage is not clear, but its occurrence has been proven by demonstration of significant amounts of fetal hemoglobin and red blood cells (RBCs) in maternal blood on the day of delivery by the Kleihauer-Betke test or by flow cytometry methods to detect fetal cells in maternal blood. If the infant has severe anemia with heart failure, emergency exchange transfusion to restore hematocrit and oxygen-carrying capacity may be needed.

Acute blood loss usually results in severe distress at birth, initially with a normal hemoglobin level, no hepatosplenomegaly, and early onset of shock. In contrast, chronic blood loss in utero produces

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**Figure 103-1** Range (mean and 95% confidence limits) of hemoglobin concentration from 10-40 wk of gestational age in normal (zone I) fetuses obtained by cordocentesis (percutaneous umbilical blood sample). Solid circles depict maternal red blood cell isoimmunization; open circles indicate hemoglobin levels in fetuses with ultrasonographic evidence of hydrops (zone III). (From Soothill PW: Cordocentesis: role in assessment of fetal condition, Clin Perinatol 16:755–770, 1989.)
marked pallor, less distress, a low hemoglobin level with microcytic indices, and, if severe, heart failure.

Anemia appearing in the first few days after birth is also most frequently a result of hemolytic disease of the newborn. Other causes are hemorrhagic disease of the newborn, bleeding from an improperly tied or clamped umbilical cord, large cephalohematoma, intracranial hemorrhage, and subcapsular bleeding from rupture of the liver, spleen, adrenals, or kidneys. Rapid decreases in hemoglobin or hematocrit values during the first few days of life may be the initial clue to these conditions.

Later in the neonatal period, delayed anemia may develop as a result of hemolytic disease of the newborn, with or without exchange transfusion or phototherapy. Congenital hemolytic anemia (spherocytosis) occasionally appears during the 1st mo of life, and hereditary nonspherocytic hemolytic anemia has been described during the neonatal period secondary to deficiency of glucose-6-phosphate dehydrogenase and pyruvate kinase. Bleeding from hemangiomata of the upper gastrointestinal tract or from ulcers caused by aberrant gastric mucosa in a Meckel diverticulum or duplication is a rare source of anemia in newborns. Repeated blood sampling of infants requiring frequent monitoring of blood gas and chemistry parameters is a common cause of anemia among hospitalized infants. Deficiency of minerals such as copper may cause anemia in infants maintained on total parenteral nutrition.

Anemia of prematurity occurs in low birthweight infants 1-3 mo after birth, is associated with hemoglobin levels <7-10 g/DL, and is clinically manifested as pallor, poor weight gain, decreased activity, tachypnea, tachycardia, and feeding problems. Repeated phlebotomy for blood tests, shortened RBC survival, rapid growth, and the physiologic effects of the transition from fetal (low Pao2 and hemoglobin saturation) to neonatal life (high Pao2 and hemoglobin saturation) contribute to anemia of prematurity. The oxygen available to neonatal tissue is lower than that in adults, but a neonate's erythropoietin response is attenuated for the degree of anemia, and as a result, hemoglobin and reticulocyte levels are low. In VLBW infants, delayed clamping of the umbilical cord with the infant held below the level of the placenta may enhance placental-infant transfusion and reduce postnatal transfusion needs. This maneuver should not delay any needed resuscitation and may lead to hyperviscosity.

**Delayed cord clamping** (30-180 sec or after cessation of cord pulsation) may be beneficial in otherwise well newborns in preventing anemia in full-term infants, with effects extending beyond the neonatal period. The benefits of delayed cord clamping persist for 2-6 mo as improved hematocrit, iron status as measured by ferritin concentration and stored iron, and a clinically important reduction in the risk of anemia in infancy. Late clamping may result in delivery of an extra 20-40 mL of blood and 30-35 mg of iron to the newborn. Polycythemia is a risk with delayed clamping but is often asymptomatic.

**Treatment** of neonatal anemia by blood transfusion depends on the severity of symptoms, the hemoglobin level, and the presence of comorbid diseases (bronchopulmonary dysplasia, cyanotic congenital heart disease, respiratory distress syndrome) that interfere with oxygen delivery. The need for treatment with blood should be balanced against the risks of transfusion, including hemolytic transfusion reactions, exposure to blood product preservatives and other potential toxins, volume overload, possible increased risk of retinopathy of prematurity and necrotizing enterocolitis, graft-versus-host (GVH) reaction, and transfusion-acquired infection (cytomegalovirus [CMV], HIV, parvovirus, hepatitis B and C) (see Chapter 474). The risk of CMV infection can be almost eliminated by the use of leukoreduced blood. In the infant who weighs <1,500 g, CMV antibody-negative leukoreduced blood should be used. The risk of acquiring HIV and hepatitis B and C viruses is reduced but not eliminated by antibody screening of donated blood. Blood-banking techniques that limit multiple donor exposure should be encouraged.

Although transfusion guidelines for preterm infants have been proposed (Table 103-2), they have not been subjected to rigorous clinical study. Nonetheless, these guidelines have led to a decline in the number of unnecessary transfusions. The use of restrictive vs more liberal transfusion guidelines has been examined in 2 randomized trials, one conducted at University of Iowa and a second multicentric trial known as the PINT (Premature Infants in Need of Transfusion) study. The restrictive guidelines in the 2 groups were generally similar. In the Iowa trial, the transfusion thresholds in the liberal- and restrictive-transfusion groups were <46% and <34%, respectively, in tracheally intubated infants receiving assisted ventilation; <38% and <28%, respectively, in infants receiving nasal continuous positive airway pressure or supplemental oxygen; and <30% and <22%, respectively, in infants breathing room air. The transfusion thresholds for the liberal groups were higher in the Iowa trial than in the PINT study. In both trials, the use of restrictive thresholds resulted in fewer transfusions and also increased the number of infants who received no transfusions at all. However, in the Iowa trial (but not in the PINT study), restrictive transfusion thresholds were associated with increases in major cranial ultrasonographic abnormalities and in the frequency of apneic spells. Although these findings need further evaluation in clinical studies, the issue of finding an appropriate transfusion threshold in premature infants remains unresolved.

Asymptomatic full-term infants with a hemoglobin level of 10 g/dL may be monitored, whereas symptomatic neonates born after abruptio placentae or with severe hemolytic disease of the newborn need immediate transfusion. Preterm infants who have repeated episodes of apnea and bradycardia despite theophylline therapy and a hemoglobin level ≤8 g/dL may benefit from RBC transfusion. In addition, infants with respiratory distress syndrome or severe bronchopulmonary dysplasia...
### Table 103-1: Normal Red Blood Cell Values from 18 Wk of Gestation to 14 Wk of Life

<table>
<thead>
<tr>
<th>AGE</th>
<th>HEMOGLOBIN (g/dL)</th>
<th>HEMATOCRIT (%)</th>
<th>MCV (µL)</th>
<th>RETICULOCYTES (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GESTATIONAL (WK)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-20*</td>
<td>11.5 ± 0.8</td>
<td>36 ± 3</td>
<td>134 ± 8.8</td>
<td>N/A</td>
</tr>
<tr>
<td>21-22*</td>
<td>12.3 ± 0.9</td>
<td>39 ± 3</td>
<td>130 ± 6.2</td>
<td>N/A</td>
</tr>
<tr>
<td>23-25*</td>
<td>12.4 ± 0.8</td>
<td>39 ± 2</td>
<td>126 ± 6.2</td>
<td>N/A</td>
</tr>
<tr>
<td>26-27</td>
<td>19.0 ± 2.5</td>
<td>62 ± 8</td>
<td>132 ± 14.4</td>
<td>9.6 ± 3.2</td>
</tr>
<tr>
<td>28-29</td>
<td>19.3 ± 1.8</td>
<td>60 ± 7</td>
<td>131 ± 13.5</td>
<td>7.5 ± 2.5</td>
</tr>
<tr>
<td>30-31</td>
<td>19.1 ± 2.2</td>
<td>60 ± 6</td>
<td>127 ± 12.7</td>
<td>5.8 ± 2.0</td>
</tr>
<tr>
<td>32-33</td>
<td>18.5 ± 2.0</td>
<td>60 ± 5</td>
<td>123 ± 15.7</td>
<td>5.0 ± 1.9</td>
</tr>
<tr>
<td>34-35</td>
<td>19.6 ± 2.1</td>
<td>61 ± 7</td>
<td>122 ± 10.0</td>
<td>3.9 ± 1.6</td>
</tr>
<tr>
<td>36-37</td>
<td>19.2 ± 1.7</td>
<td>64 ± 7</td>
<td>121 ± 12.5</td>
<td>4.2 ± 1.8</td>
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<tr>
<td>38-40</td>
<td>19.3 ± 2.2</td>
<td>61 ± 7</td>
<td>119 ± 9.4</td>
<td>3.2 ± 1.4</td>
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<td>POSTNATAL (DAYS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>19.0 ± 2.2</td>
<td>61 ± 7</td>
<td>119 ± 9.4</td>
<td>3.2 ± 1.4</td>
</tr>
<tr>
<td>2</td>
<td>19.0 ± 1.9</td>
<td>60 ± 6</td>
<td>115 ± 7.0</td>
<td>3.2 ± 1.3</td>
</tr>
<tr>
<td>3</td>
<td>18.7 ± 3.4</td>
<td>62 ± 9</td>
<td>116 ± 5.3</td>
<td>2.8 ± 1.7</td>
</tr>
<tr>
<td>4</td>
<td>18.6 ± 2.1</td>
<td>57 ± 8</td>
<td>114 ± 7.6</td>
<td>1.8 ± 1.1</td>
</tr>
<tr>
<td>5</td>
<td>17.6 ± 1.1</td>
<td>57 ± 7</td>
<td>114 ± 8.9</td>
<td>1.2 ± 0.2</td>
</tr>
<tr>
<td>6</td>
<td>17.4 ± 2.2</td>
<td>54 ± 7</td>
<td>113 ± 10.0</td>
<td>0.6 ± 0.2</td>
</tr>
<tr>
<td>7</td>
<td>17.9 ± 2.5</td>
<td>56 ± 9</td>
<td>118 ± 11.2</td>
<td>0.5 ± 0.4</td>
</tr>
<tr>
<td>POSTNATAL (WK)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>17.3 ± 2.3</td>
<td>54 ± 8</td>
<td>112 ± 19.0</td>
<td>0.5 ± 0.3</td>
</tr>
<tr>
<td>2-3</td>
<td>15.6 ± 2.6</td>
<td>46 ± 7</td>
<td>111 ± 8.2</td>
<td>0.8 ± 0.6</td>
</tr>
<tr>
<td>3-4</td>
<td>14.2 ± 2.1</td>
<td>43 ± 6</td>
<td>105 ± 7.5</td>
<td>0.6 ± 0.3</td>
</tr>
<tr>
<td>4-5</td>
<td>12.7 ± 1.6</td>
<td>36 ± 5</td>
<td>101 ± 8.1</td>
<td>0.9 ± 0.8</td>
</tr>
<tr>
<td>5-6</td>
<td>11.9 ± 1.5</td>
<td>36 ± 6</td>
<td>102 ± 10.2</td>
<td>1.0 ± 0.7</td>
</tr>
<tr>
<td>6-7</td>
<td>12.0 ± 1.5</td>
<td>36 ± 5</td>
<td>105 ± 12.0</td>
<td>1.2 ± 0.7</td>
</tr>
<tr>
<td>7-8</td>
<td>11.1 ± 1.1</td>
<td>33 ± 4</td>
<td>100 ± 13.0</td>
<td>1.5 ± 0.7</td>
</tr>
<tr>
<td>8-9</td>
<td>10.7 ± 0.9</td>
<td>31 ± 3</td>
<td>93 ± 12.0</td>
<td>1.8 ± 1.0</td>
</tr>
<tr>
<td>9-10</td>
<td>11.2 ± 0.9</td>
<td>32 ± 3</td>
<td>91 ± 9.3</td>
<td>1.2 ± 0.6</td>
</tr>
<tr>
<td>10-11</td>
<td>11.4 ± 0.9</td>
<td>34 ± 2</td>
<td>91 ± 7.7</td>
<td>1.2 ± 0.7</td>
</tr>
<tr>
<td>11-12</td>
<td>11.3 ± 0.9</td>
<td>33 ± 3</td>
<td>88 ± 7.9</td>
<td>0.7 ± 0.3</td>
</tr>
<tr>
<td>12-14</td>
<td>11.9</td>
<td>37</td>
<td>86.8</td>
<td>0.9</td>
</tr>
</tbody>
</table>

*Based on samples collected in utero. Results expressed as mean value ±1 standard deviation from the mean except for postnatal weeks 12-14 in which only the mean value is given.


### Table 103-2: Transfusion Protocol

<table>
<thead>
<tr>
<th>HEMATOCRIT (%)</th>
<th>HEMOGLOBIN (g/dL)</th>
<th>RESPIRATORY SUPPORT AND/OR SYMPTOMS</th>
<th>TRANSFUSION VOLUME</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤35</td>
<td>≤11</td>
<td>Infants requiring moderate or significant mechanical ventilation (mean arterial pressure &gt;8 cm H$_2$O and FIO$_2$ &gt;0.4)</td>
<td>15 mL/kg PRBCs* over 2-4 hr</td>
</tr>
<tr>
<td>≤30</td>
<td>≤10</td>
<td>Infants requiring minimal respiratory support (any mechanical ventilation or endotracheal/nasal continuous positive airway pressure &gt;6 cm H$_2$O and FIO$_2$ ≤0.4)</td>
<td>15 mL/kg PRBCs over 2-4 hr</td>
</tr>
<tr>
<td>≤25</td>
<td>≤8</td>
<td>Infants not requiring mechanical ventilation but who are receiving supplemental O$_2$ or CPAP with an FIO$_2$ ≤0.4 and in whom 1 or more of the following is present:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ≤24 hr of tachycardia (heart rate &gt;180 beats/min) or tachypnea (respiratory rate &gt;80 breaths/min)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• An increased oxygen requirement from the previous 48 hr, defined as a 24-fold increase in nasal canula flow (i.e., from 0.25 to 1 L/min) or an increase in nasal CPAP ≥20% from the previous 48 hr (i.e., 5-6 cm H$_2$O)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Weight gain &lt;10 g/kg/day over the previous 4 days while infant is receiving ≥100 kcal/kg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• An increase in episodes of apnea and bradycardia (&gt;9 episodes in a 24-hr period or ≥2 episodes in 24 hr requiring bag and mask ventilation) while infant is receiving therapeutic doses of methylxanthines</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Undergoing surgery</td>
<td></td>
</tr>
<tr>
<td>≤20</td>
<td>≤7</td>
<td>Asymptomatic and an absolute reticulocyte count &lt;100,000 cells/μL</td>
<td>20 mL/kg PRBCs over 2-4 hr (divide into 2 10-mL/kg volumes if infant is fluid sensitive)</td>
</tr>
</tbody>
</table>

*RBCs should be irradiated prior to transfusion.

CPAP, continuous positive airway pressure; FIO$_2$, fractional inspired oxygen; PRBCs, packed red blood cells.

may need hemoglobin levels of 12-14 g/dL to improve oxygen delivery. No transfusion is needed to replace blood removed for testing or for mild asymptomatic anemia. Asymptomatic neonates with reticulocytopenia and hemoglobin levels ≤ 7 g/dL may require transfusion; if a transfusion is not provided, close observation is essential. Packed RBC transfusion (10-20 mL/kg) is given at a rate of 2-3 mL/kg/hr to raise the hemoglobin concentration; 2 mL/kg raises the hemoglobin level 0.5-1 g/dL. Hemorrhage should be treated with whole blood if available; alternatively, fluid resuscitation is initiated, followed by packed RBC transfusion.

Recombinant human erythropoietin (rHuEPO) may be considered in the treatment of chronic or anticipated anemia in an attempt to decrease or eliminate transfusions when families, for religious reasons, request all possible measures to avoid transfusions. Therapy with rHuEPO must be supplemented with oral iron. Doses and regimens vary. In anemia of prematurity, rHuEPO does not provide a major reduction in transfusion requirements or the number of donors; therefore, routine use of erythropoietin in VLBW infants is not recommended. Early initiation of rHuEPO therapy may produce a small reduction in the total transfusion volume per infant. There were concerns about an increased risk of severe retinopathy of prematurity in the rHuEPO group. The effects of late initiation of rHuEPO (≥8 days) have also been associated with small reductions in the total blood volume transfused per infant and the number of transfusions per infant. In pilot studies, a single-dose treatment with darbepoetin alfa, a long-acting form of recombinant erythropoietin, has shown promise as a stimulant of erythropoiesis in convalescing premature infants.

Bibliography is available at Expert Consult.

103.2 Hemolytic Disease of the Newborn (Erythroblastosis Fetalis)
Akhil Maheshwari and Waldemar A. Carlo

Erythroblastosis fetalis is caused by the transplacental passage of maternal antibody active against paternal RBC antigens of the infant and is characterized by an increased rate of RBC destruction. It is an important cause of anemia and jaundice in newborn infants despite the development of a method of preventing maternal isoimmunization by Rh antigens. Although more than 60 different RBC antigens are capable of eliciting an antibody response, significant disease is associated primarily with the D antigen of the Rh group and with incompatibility of ABO factors. Rarely, hemolytic disease may be caused by C or E antigens or by other RBC antigens, such as C\(^a\), C\(^b\), D\(^e\), K (Kell), M, Duffy, S, P, MNS, Xg, Lutheran, Diego, and Kidd. Anti-Lewis antibodies do not cause disease.

HEMOLYTIC DISEASE OF THE NEWBORN CAUSED BY RH INCOMPATIBILITY

The Rh antigenic determinants are genetically transmitted from each parent, determine the Rh type, and direct the production of a number of blood group factors (C, c, D, d, E, and e). Each factor can elicit a specific antibody response under suitable conditions; 90% are caused by D antigen and the remainder to C or E antigen.

Pathogenesis
Isooimmune hemolytic disease from D antigen is approximately 3 times more frequent among white persons than among black persons. When Rh-positive blood is infused into an Rh-negative woman through error, or when small quantities (usually >1 mL) of Rh-positive fetal blood containing D antigen inherited from an Rh-positive father enter the maternal circulation during pregnancy, with spontaneous or induced abortion, or at delivery, antibody formation against D antigen may be induced in the unsensitized Rh-negative recipient mother. Once sensitization has taken place, considerably smaller doses of antigen can stimulate an increase in antibody titer. Initially, a rise in immunoglobulin (Ig) M antibody occurs, which is later replaced by IgG antibody; the latter readily crosses the placenta to cause hemolytic manifestations.

Hemolytic disease rarely occurs during a first pregnancy because transfusion of Rh-positive fetal blood into an Rh-negative mother occurs near the time of delivery, too late for the mother to become sensitized and transmit antibody to her infant before delivery. The facts that 55% of Rh-positive fathers are heterozygous (D/d) and may have Rh-negative offspring and that fetal-to-maternal transfusion occurs in only 50% of pregnancies, reduce the chance of sensitization, as does small family size, in which the opportunities for its reoccurrence are reduced. The disparity between the numbers of incompatible versus alloimmunized maternal-fetal pairs can also be the result of a threshold effect of fetomaternal transfusions (a certain amount of the immunizing blood cell antigen is required to activate the maternal immune system), the type of antibody response (IgG antibodies are more efficiently transferred across the placenta to the fetus), differential immunogenicity of blood group antigens, and differences in maternal immune response, presumably related to differences in the efficiency of antigen presentation by various major histocompatibility loci. Thus, the overall incidence of isoimmunization of Rh-negative mothers at risk is low, with antibody to antigen D detected in >10% of those studied, even after five or more pregnancies; only approximately 5% ever have babies with hemolytic disease.

When the mother and fetus are also incompatible with respect to group A or B, the mother is partially protected against sensitization by the rapid removal of Rh-positive cells from her circulation by her preexisting anti-A or anti-B antibodies, which are IgM antibodies and do not cross the placenta. Once a mother has been sensitized, her infant is likely to have hemolytic disease. The severity of Rh illness worsens with successive pregnancies. The possibility that the first affected infant after sensitization may represent the end of the mother’s childbearing potential for Rh-positive infants argues urgently for the prevention of sensitization. The injection of anti-D gammaglobulin (RhoGAM) into the mother immediately after the delivery of each Rh-positive infant has been a successful strategy to reduce Rh hemolytic disease.

Clinical Manifestations
A wide spectrum of hemolytic disease occurs in affected infants born to sensitized mothers, depending on the nature of the individual immune response. The severity of the disease may range from only laboratory evidence of mild hemolysis (15% of cases) to severe anemia with compensatory hyperplasia of erythropoietic tissue leading to massive enlargement of the liver and spleen. When the compensatory capacity of the hematopoietic system is exceeded, profound anemia occurs and results in pallor, signs of cardiac decompensation (cardiomegaly, respiratory distress), massive anasarca, and circulatory collapse. This clinical picture of excessive abnormal fluid in 2 or more fetal compartments (skin, pleura, pericardium, placenta, peritoneum, amniotic fluid), termed hydrops fetalis, frequently results in death in utero or shortly after birth. With the use of RhoGAM to prevent Rh sensitization, nonimmune (nonhemolytic) conditions have become frequent causes of hydrops (Table 103-3). The severity of hydrops is related to the level of anemia and the degree of reduction in serum albumin (oncotic pressure), which is partly a result of hepatic dysfunction. Alternatively, heart failure may increase right heart pressure, with the subsequent development of edema and ascites. Failure to initiate spontaneous effective ventilation because of pulmonary edema or bilateral pleural effusions results in birth asphyxia; after successful resuscitation, severe respiratory distress may develop. Petechiae, purpura, and thrombocytopenia may also be present in severe cases as a result of decreased platelet production or the presence of concurrent disseminated intravascular coagulation.

Jaundice may be absent at birth because of placental clearance of lipid-soluble unconjugated bilirubin, but in severe cases, bilirubin pigments stain the amniotic fluid, cord, and vernix caseosa yellow. Jaundice is generally evident on the 1st day of life because the infant's bilirubin-conjugating and excretory systems are unable to cope with the load resulting from massive hemolysis. Indirect-reacting bilirubin...
Bibliography


The hemolysis may be masked by the previous intrauterine transfusion, and the anemia and hydrops resolve before birth. Anemia from continuing vein transfusions in utero may also have a benign postnatal course if and its effects on hepatic function. Infants treated with intraumbilical able) cord levels of bilirubin, reflecting the severity of the hemolysis fetal anemia). Such infants usually have very high (but extremely vari-

to hyperinsulinism and hypertrophy of the pancreatic islet cells in infants with severe isoimmune hemolytic disease and may be related complications (hypoxia, acidosis). Hypoglycemia occurs frequently in although the risk in an individual patient may be affected by other
greater than from comparable nonhemolytic hyperbilirubinemia,
The risk of development of kernicterus from hemolytic disease is high levels and present a significant risk of bilirubin encephalopathy. therefore accumulates postnataally and may rapidly reach extremely high levels and present a significant risk of bilirubin encephalopathy. The risk of development of kernicterus from hemolytic disease is greater than from comparable nonhemolytic hyperbilirubinemia, although the risk in an individual patient may be affected by other complications (hypoxia, acidosis). Hypoglycemia occurs frequently in infants with severe isoimmune hemolytic disease and may be related to hyperinsulinism and hypertrophy of the pancreatic islet cells in these infants.

Infants born after intrauterine transfusion for prenatally diagnosed erythroblastosis may be severely affected because the indications for transfusion are evidence of already severe disease in utero (hydrops, fetal anemia). Such infants usually have very high (but extremely variable) cord levels of bilirubin, reflecting the severity of the hemolysis and its effects on hepatic function. Infants treated with intraumbilical vein transfusions in utero may also have a benign postnatal course if the anemia and hydrops resolve before birth. Anemia from continuing hemolysis may be masked by the previous intrauterine transfusion, and the clinical manifestations of erythroblastosis may be superimposed on various degrees of immaturity resulting from spontaneous or induced premature delivery.

**Laboratory Data**
Before treatment, the direct Coombs test result is usually positive and anemia is generally present. The cord blood hemoglobin content varies and is usually proportional to the severity of the disease; with hydrops fetalis it may be as low as 3–4 g/dL. Alternatively, despite hemolysis, it may be within the normal range because of compensatory bone marrow and extramedullary hematopoiesis. The blood smear typically shows polychromasia and a marked increase in nucleated RBCs. The reticulocyte count is increased. The white blood cell count is usually normal but may be elevated; thrombocytopenia may develop in severe cases. Cord bilirubin is generally between 3 and 5 mg/dL; the direct-reacting (conjugated) bilirubin content may also be elevated, especially if there was an intrauterine transfusion. Indirect- reacting bilirubin content rises rapidly to high levels in the 1st 6 hr of life.

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**Table 103-3**  
**Etiology of Hydrops Fetalis**

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>DISORDER(S)</th>
</tr>
</thead>
</table>
| Anemia   | Immune (Rh, Kell) hemolysis  
|          | α-Thalassemia  
|          | Red blood cell enzyme deficiencies (glucose-6-phosphate dehydrogenase)  
|          | Fetomaternal hemorrhage  
|          | Donor in twin-to-twin transfusion  
|          | Diamond-Blackfan syndrome  
| Cardiac dyshrhythmias | Supraventricular tachycardia  
|          | Atrial flutter  
|          | Congenital heart block  
| Structural heart lesions | Premature closure of foramen ovale  
|          | Tricuspid insufficiency  
|          | Hypoplastic left heart  
|          | Endocardial cushion defect  
|          | Cardiomyopathy  
|          | Endocardial fibroelastosis  
|          | Tuberous sclerosis with cardiac rhabdomyoma  
|          | Pericardial teratoma  
| Vascular | Chorioangioma of placenta, chorionic vessels, or umbilical vessels  
|          | Umbilical artery aneurysm  
|          | Angiomyoma of umbilical cord  
|          | True knot of umbilical cord  
|          | Hepatic hemangioma  
|          | Cerebral arteriovenous malformation (aneurysm of vein of Galen)  
|          | Angiooosteohypertrophy (Klippel-Trénaunay syndrome)  
|          | Thrombosis of renal or umbilical vein or inferior vena cava  
|          | Recipient in twin-to-twin transfusion  
| Lymphatic | Lymphangiectasia  
|          | Cystic hygroma  
|          | Chylothorax, chylous ascites  
|          | Noonan syndrome  
|          | Multiple pterygium syndrome  
| Central nervous system | Absent corpus callosum  
|          | Encephalocele  
|          | Intracranial hemorrhage  
|          | Holoprosencephaly  
| Thoracic lesions | Cystic adenomatoid malformation of lung  
|          | Mediastinal teratoma  
|          | Diaphragmatic hernia  
|          | Sequestered lung  
| Tumors and storage diseases | Teratomas  
|          | Choriocarcinoma  
|          | Sacrococcygeal teratoma  
| Congenital infections | Neuroblastoma  
|          | Hepatoblastoma  
|          | Gaucher disease  
|          | Niemann-Pick disease  
|          | Mucolipidosis  
|          | GM1 gangliosidosis  
|          | Mucopolysaccharidosis  
| Chromosome abnormalities | Trisomy 13, 15, 16, 18, 21  
|          | XXXY, 45XO  
|          | Partial duplication of chromosomes 11, 15, 17, 18  
|          | Partial deletion of chromosomes 13, 18  
|          | Trisomy 21  
|          | Tetraplody  
| Bone diseases | Osteogenesis imperfecta  
|          | Asphyxiating thoracic dystrophy  
|          | Skeletal dysplasias  
| Others | Bowel obstruction with perforation and meconium peritonitis, volvulus  
|          | Hepatic fibrosis  
|          | Beckwith-Wiedemann syndrome  
|          | Prune-belly syndrome  
|          | Congenital nephrosis  
|          | Infant of a diabetic mother  
|          | Myotonic dystrophy  
|          | Neu-Laxova syndrome  
|          | Maternal therapy with indomethacin  
|          | Fetal akinesia  
| Idiopathic | Multiple congenital anomaly syndromes  

*The incidence of nonimmune (nonhemolytic) hydrops fetalis is 1/2,000–1/3,500 live births.  
After intrauterine transfusions, cord blood may show a normal hemoglobin concentration, negative direct Coombs test result, predominantly type O Rh-negative adult RBCs, and relatively normal smear findings.

**Diagnosis**

Definitive diagnosis of erythroblastosis fetalis requires demonstration of blood group incompatibility and corresponding antibody bound to the infant’s RBCs.

**Antenatal Diagnosis**

In Rh-negative women, a history of previous transfusions, abortion, or pregnancy should suggest the possibility of sensitization. Expectant parents’ blood types should be tested for potential incompatibility, and the maternal titer of IgG antibodies to D antigen should be assayed at 12-16, 28-32, and 36 wk of gestation. Fetal Rh status may be determined by isolating fetal cells or fetal DNA (plasma) from the maternal circulation. The presence of elevated antibody titers at the beginning of pregnancy, a rapid rise in titer, or a titer of 1:64 or greater suggests significant hemolytic disease, although the exact titer correlates poorly with the severity of disease. If a mother is found to have antibody against D antigen at a titer of 1:16 (15 IU/mL in Europe) or greater at any time during a subsequent pregnancy, the severity of fetal disease should be monitored by Doppler ultrasonography of the middle cerebral artery and then percutaneous umbilical blood sampling (PUBS) if indicated (see Chapter 96). If the mother has a history of a previously affected infant or a stillbirth, an Rh-positive infant is usually equally or more severely affected than the previous infant, and the severity of disease in the fetus should be monitored.

Assessment of the fetus may require information obtained from ultrasonography and PUBS. Real-time ultrasonography is used to detect the progression of disease, with hydrops defined as skin or scalp edema, pleural or pericardial effusions, and ascites. Early ultrasonographic signs of hydrops include organomegaly (liver, spleen, heart), the double–bowel wall sign (bowel edema), and placental thickening. Progression to polyhydramnios, ascites, pleural or pericardial effusions, and skin or scalp edema may then follow. If pleural effusions precede ascites and hydrops by a significant time, causes other than fetal anemia should be suspected (see Table 96-2 in Chapter 96). Extramedullary hematopoiesis and, less so, hepatic congestion compress the intrahepatic vessels and produce venous stasis with portal hypertension, hepatocellular dysfunction, and decreased albumin synthesis.

Hydrops is present with a fetal hemoglobin level <5 g/dL, frequent with a level <7 g/dL, and variable with levels between 7 and 9 g/dL. Real-time ultrasonography predicts fetal well-being by means of the biophysical profile (see Table 96-2 in Chapter 96), whereas Doppler ultrasonography assesses fetal distress by demonstrating increased vascular resistance in fetal arteries (middle cerebral). In pregnancies with ultrasonographic evidence of hemolysis (hepatosplenomegaly), early or late hydrops, or fetal distress, further and more direct assessment of fetal hemolysis should be performed.

Aminioacetate was classically used to assess fetal hemolysis. Hemolysis of fetal RBCs produces hyperbilirubinemia before the onset of severe anemia. Bilirubin is cleared by the placenta, but a significant proportion enters the amniotic fluid and can be measured by spectrophotometry. Ultrasonographically guided transabdominal aspiration of amniotic fluid may be performed as early as 18-20 wk of gestation. Spectrophotometric scanning of amniotic fluid wavelengths demonstrates a positive optical density deviation of absorption for bilirubin from normal at 450 nm. Aminioacetate and cordocentesis are invasive procedures with risks to both the fetus and mother, including fetal death, bleeding, or bradycardia, worsening of alloimmunization, premature rupture of membranes, preterm labor, and choioamnionitis. *Noninvasive measurements to detect fetal anemia are desirable.* In fetuses without hydrops, moderate to severe anemia can be detected noninvasively by demonstration of an increase in the peak velocity of systolic blood flow in the middle cerebral artery by Doppler ultrasonography.

**Postnatal Diagnosis**

Immediately after the birth of any infant to an Rh-negative woman, blood from the umbilical cord or from the infant should be examined for ABO blood group, Rh type, hemoglobin, and reaction to the direct Coombs test. If the Coombs test result is positive, a baseline serum bilirubin level should be measured, and a commercially available RBC panel should be used to identify RBC antibodies present in the mother’s serum, both tests being performed not only to establish the diagnosis but also to ensure selection of the most compatible blood for exchange transfusion should it be necessary. The direct Coombs test result is usually strongly positive in clinically affected infants and may remain so for a few days up to several months.

**Treatment**

The main goals of therapy are to (1) prevent intrauterine or extrauterine death from severe anemia and hypoxia, and (2) avoid neurotoxicity from hyperbilirubinemia.

**Treatment of an Unborn Infant**

Survival of severely affected fetuses has been improved by the use of fetal ultrasonography to identify the need for in utero transfusion. Intravascular (umbilical vein) transfusion of packed RBCs is the treatment of choice for fetal anemia, replacing intrauterine transfusion into the fetal peritoneal cavity. Hydrops or fetal anemia (hematocrit <30%) is an indication for umbilical vein transfusion in infants with pulmonary immaturity (see Fig. 103-1). *Intravascular fetal transfusion* is facilitated by maternal and hence fetal sedation with diazepam and by fetal paralysis with pancuronium. Packed RBCs are given by slow-push infusion after being cross-matched against the mother’s serum. The cells should be obtained from a CMV-negative donor and irradiated to kill lymphocytes to avoid GVH disease. Of note, leukoreduction alone (without irradiation) does not prevent GVH disease. Transfusions should achieve a posttransfusion hematocrit of 45-55% and can be repeated every 3-5 wk. Indications for delivery include pulmonary maturity, fetal distress, complications of PUBS, and 35-37 wk of gestation. The survival rate for intrauterine transfusions is 89%; the complication rate is 3%. Complications include rupture of the membranes and preterm delivery, infection, fetal distress requiring emergency cesarean section, and perinatal death.

**Treatment of a Liveborn Infant**

The birth should be attended by a physician skilled in neonatal resuscitation. Fresh, low-titer, group O, leukoreduced, and irradiated Rh-negative blood cross-matched against maternal serum should be immediately available. If clinical signs of severe hemolytic anemia (pallor, hepatosplenomegaly, edema, petechiae, ascites) are evident at birth, immediate resuscitation and supportive therapy, temperature stabilization, and monitoring before proceeding with exchange transfusion may save some severely affected infants. Such therapy should include correction of acidosis with 1-2 mEq/kg of sodium bicarbonate; a small transfusion of compatible packed RBCs to correct anemia; volume expansion for hypotension, especially in those with hydrops; and provision of assisted ventilation for respiratory failure.

**Exchange Transfusion**

When an infant’s clinical condition at birth does not require an immediate full or partial exchange transfusion, the decision to perform one should be based on a judgment that the infant has a high risk of rapid development of a dangerous degree of anemia or hyperbilirubinemia. Cord hemoglobin value of 10 g/dL or less and bilirubin concentration of 5 mg/dL or more suggest severe hemolysis but inconsistently predict the need for exchange transfusion. Some physicians consider previous kernicterus or severe erythroblastosis in a sibling, reticulocyte counts
and hypoxic during exchange transfusions. Symptomatic hypoglycemia may occur before or during an exchange transfusion in moderately to severely affected infants; it may also occur 1-3 hr after exchange. Acute complications, noted in 5-10% of infants, include transient bradycardia with or without calcium infusion, cyanosis, transient vasospasm, thrombosis, apnea with bradycardia requiring resuscitation, and death. Infectious risks include CMV, HIV, and hepatitis. Necrotizing enterocolitis is a rare complication of exchange transfusion.

The risk of death from an exchange transfusion performed by an experienced physician is 0.3/100 procedures. With the decreasing use of this procedure because of the use of phototherapy and prevention of sensitization, the general level of physician competence is diminishing. Thus, it is best if this procedure is performed in experienced neonatal referral centers.

After exchange transfusion, the bilirubin level must be determined at frequent intervals (every 4-8 hr) because bilirubin may rebound 40-50% within hours. Repeated exchange transfusions should be carried out to keep the indirect fraction from exceeding the levels indicated in Table 102-7 in Chapter 102 for preterm infants and 20 mg/dL for term infants. Symptoms suggestive of kernicterus are mandatory indications for exchange transfusion at any time.

### Intravenous Immunoglobulin

Early administration of intravenous immunoglobulin (IVIG) may reduce hemolysis, peak serum bilirubin levels, and the need for exchange transfusions. IVIG administration reduces the need for exchange transfusion, the duration of phototherapy, and the length of hospitalization. A dose of 0.5-1 g/kg may be used.

### Late Complications

Infants who have hemolytic disease or who have had an exchange or an intrauterine transfusion must be observed carefully for the development of anemia and cholestasis. Late anemia may be hemolytic or hyporegenerative. Treatment with supplemental iron, blood transfusion, or erythropoietin may be indicated. A mild GVH reaction may manifest as diarrhea, rash, hepatitis, or eosinophilia.

### Insipidated bile syndrome

Refers to the rare occurrence of persistent icterus in association with significant elevations in direct and indirect bilirubin levels in infants with hemolytic disease. The cause is unclear, but the jaundice clears spontaneously within a few weeks or months.

### Portal vein thrombosis

And portal hypertension may occur in children who have been subjected to exchange transfusion as newborn infants. It is probably associated with prolonged, traumatic, or septic umbilical vein catheterization.

### Prevention of Rh Sensitization

The risk of initial sensitization of Rh-negative mothers has been reduced to less than 1% by the intramuscular injection of 300 μg of human anti-D globulin (1 mL of RhoGAM) within 72 hr of delivery of an Rh-positive infant, ectopic pregnancy, abdominal trauma in pregnancy, amniocentesis, choriocarcinoid villus biopsy, or abortion. This quantity is sufficient to eliminate ~10 mL of potentially antigenic fetal cells from the maternal circulation. Large fetal-to-maternal transfers of blood may require proportionately more human anti-D globulin. RhoGAM administration of human anti-D globulin at 28-32 wk and again at birth (40 wk) is more effective than a single dose. The use of this technique, combined with improved methods of detecting maternal sensitization and measuring the extent of fetal-to-maternal transfusion, plus the use of fewer obstetric procedures that increase the risk of such fetal-to-maternal bleeding (version, manual separation of the placenta), should further reduce the incidence of erythroblastosis fetalis.

### Hemolytic Disease of the Newborn Caused by Blood Group A and B Incompatibility

ABO incompatibility is the most common cause of hemolytic disease of the newborn. Approximately 15% of live births are at risk, but...
manifestations of disease develop in only 0.3-2.2%. Major blood group incompatibility between the mother and fetus generally results in milder disease than Rh incompatibility does. Maternal antibody may be formed against B cells if the mother is type A or against A cells if the mother is type B. Usually, the mother is type O and the infant is type A or B. Although ABO incompatibility occurs in 20-25% of pregnancies, hemolytic disease develops in only 10% of the offspring in such pregnancies, and the infants are generally type A, which is more antigenic than A. Low antigenicity of the ABO factors in the fetus and transfusions with type O blood of the same Rh type as the infant may rate of hemolysis and the need for exchange transfusion. Exchange

Chapter 102.4). In severe cases, IVIG administration can reduce the treatment administered.

nucleated RBCs. In 10-20% of affected infants, the unconjugated serum

10-15%, with extensive polychromasia and increased numbers of nucleated RBCs. In 10-20% of affected infants, the unconjugated serum bilirubin level may reach 20 mg/dL or more unless phototherapy is administered.

Diagnosis

A presumptive diagnosis is based on the presence of ABO incompatibility, a weakly to moderately positive direct Coombs test result, and spherocytosis in the blood smear, which may at times suggest the presence of hereditary spherocytosis. Hyperbilirubinemia is often the only other laboratory abnormality. The hemoglobin level is usually normal but may be as low as 10-12 g/dL. Reticulocytes may be increased to 10-15%, with extensive polychromasia and increased numbers of nucleated RBCs. In 10-20% of affected infants, the unconjugated serum bilirubin level may reach 20 mg/dL or more unless phototherapy is administered.

Treatment

Phototherapy may be effective in lowering serum bilirubin levels (see Chapter 102.4). In severe cases, IVIG administration can reduce the rate of hemolysis and the need for exchange transfusion. Exchange transfusions with type O blood of the same Rh type as the infant may be needed in some cases to correct dangerous degrees of anemia or hyperbilirubinemia. Indications for this procedure are similar to those previously described for hemolytic disease caused by Rh incompatibility. Some infants with ABO hemolytic disease may require transfusion of packed RBCs at several weeks of age because of slowly progressive anemia. Postdischarge monitoring of hemoglobin or hematocrit is essential in newborns with ABO hemolytic disease.

OTHER FORMS OF HEMOLYTIC DISEASE

Blood group incompatibilities other than Rh or ABO account for <5% of hemolytic disease of the newborn. The direct Coombs test result is invariably positive, and exchange transfusion may be indicated for hyperbilirubinemia and anemia. Hemolytic disease, anemia, and hydrops fetalis as a result of anti-Kell antibodies are not predictable from the previous obstetric history, amniotic fluid bilirubin determinants, or the maternal antibody titer. Erythroid suppression may contribute to the anemia; PUBS is beneficial in actually measuring the fetal hematocrit. Kell-alloimmunized infants often have inappropriately low numbers of circulating reticulocytes in comparison with other forms of hemolytic disease, which can cause difficulties in the laboratory confirmation of the hemolytic etiology of hyperbilirubinemia. The clinical characteristics of hemolytic disease caused by Rh, ABO, and Kell antigen systems are summarized in Table 103-4.

Bibliography is available at Expert Consult.

103.3 Plethora in the Newborn Infant (Polycythemia)

Akhil Maheshwari and Waldemar A. Carlo

See also Chapter 467.

Plethora, a ruddy, deep red-purple appearance associated with a high hematocrit, is often due to polycythemia, defined as a central hematocrit of 65% or higher. Peripheral (heelstick) hematocrit values are higher than central values, whereas Coulter counter results are lower than hematocrit values determined by microcentrifugation. The incidence of neonatal polycythemia is increased at high altitudes (5% in Denver vs. 1.6% in Texas); in postmature (3%) versus term (1-2%) infants; in small for gestational age (8%) versus large for gestational age (3%) versus average for gestational age (1-2%) infants; during the 1st day of life (peak, 2-3 hr); in the recipient infant of a twin–twin transfusion; after delayed clamping of the umbilical cord; in infants of diabetic mothers; in trisomy 13, 18, or 21; in adrenogenital syndrome;
Bibliography


in neonatal Graves disease; in hypothyroidism; in infants of hypertensive mothers or those on propranolol; and in Beckwith-Wiedemann syndrome. Infants of diabetic or hypertensive mothers and those with growth restriction may have been exposed to chronic fetal hypoxia, which stimulates erythropoietin production and increases RBC production.

Clinical manifestations include irritability, lethargy, tachypnea, respiratory distress, cyanosis, feeding disturbances, hyperbilirubinemia, hypoglycemia, and thrombocytopenia. Severe complications include seizures, stroke, pulmonary hypertension, necrotizing enterocolitis, renal vein thrombosis, and renal failure. Many affected infants are asymptomatic. Hyperviscosity is present in many infants with central hematocrit values of 65% or higher and accounts for the symptoms of polycythemia. Hyperviscosity determined at constant shear rates (11.5 sec⁻¹) is present when whole blood viscosity is >18 cycles/sec. Hyperviscosity is accentuated because neonatal RBCs have decreased deformability and filterability, which predispose to stasis in the microcirculation.

The treatment of polycythemia is controversial. Asymptomatic infants whose central hematocrits are between 60% and 70% can be monitored closely and aggressively hydrated with adequate enteral intake or administration of intravenous fluids. Treatment of symptomatic polycythemic newborns is partial exchange transfusion (with normal saline). A partial exchange transfusion should be considered if the hematocrit is ≥70-75% or even lower if signs of hyperviscosity are present. Partial exchange transfusion lowers the Hematocrit and viscosity and improves acute symptoms, but may not affect long-term outcome in these infants. The volume to be exchanged is calculated from the following formula:

\[ \text{Volume of exchange (mL)} = \frac{\text{Blood volume} \times (\text{Observed} - \text{Desired hematocrit})}{\text{Observed hematocrit}} \]

Infants treated with partial exchange may be at increased risk of necrotizing enterocolitis and should be carefully monitored. The long-term prognosis of polycythemic infants is unclear. Reported adverse outcomes include speech deficits, abnormal fine motor control, reduced IQ, school problems, and other neurologic abnormalities. The underlying etiology (chronic intrauterine hypoxia) and hyperviscosity is thought to contribute to adverse outcomes. It is unclear whether partial exchange transfusion improves the long-term outcome. Most asymptomatic infants develop normally.

Bibliography is available at Expert Consult.

### Table 103-5 Hemorrhagic Disease of the Newborn

<table>
<thead>
<tr>
<th>Age</th>
<th>EARLY-ONSET DISEASE</th>
<th>CLASSIC DISEASE</th>
<th>LATE-ONSET DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-24 hr</td>
<td>2-7 days</td>
<td>1-6 mo</td>
</tr>
<tr>
<td>Site of hemorrhage</td>
<td>Cephalohematoma</td>
<td>Gastrointestinal</td>
<td>Intracranial</td>
</tr>
<tr>
<td></td>
<td>Subgaleal</td>
<td>Ear-nose-throat-mucosal</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td></td>
<td>Intracranial</td>
<td>Intracranial</td>
<td>Ear-nose-throat-mucosal</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal</td>
<td>Circumcision</td>
<td>Injection sites</td>
</tr>
<tr>
<td></td>
<td>Umbilicus</td>
<td>Cutaneous</td>
<td>Thoracic</td>
</tr>
<tr>
<td></td>
<td>Intraabdominal</td>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Etiology/risk</td>
<td>Maternal drugs (phenobarbital, phenytoin, warfarin, rifampin, isoniazid) that interfere with vitamin K</td>
<td>Vitamin K deficiency</td>
<td>Cholestasis—malabsorption of vitamin K (biliary atresia, cystic fibrosis, hepatitis)</td>
</tr>
<tr>
<td></td>
<td>Inherited coagulopathy</td>
<td>Breastfeeding</td>
<td>Abetalipoprotein deficiency</td>
</tr>
<tr>
<td>Prevention</td>
<td>Possibly, administrations of vitamin K to infant at birth or to mother (20 mg) before birth</td>
<td>Prevented by parenteral vitamin K at birth</td>
<td>Idiopathic in Asian breastfed infants</td>
</tr>
<tr>
<td></td>
<td>Avoid high-risk medications</td>
<td>Oral vitamin K regimens require repeated dosing over time</td>
<td>Warfarin ingestion</td>
</tr>
<tr>
<td>Incidence</td>
<td>Very rare</td>
<td>≈ 2% if infant not given vitamin K</td>
<td>Dependent on primary disease</td>
</tr>
</tbody>
</table>

### 103.4 Hemorrhage in the Newborn Infant

Akhil Maheshwari and Waldemar A. Carlo

**HEMORRHAGIC DISEASE OF THE NEWBORN**

A moderate decrease in factors II, VII, IX, and X normally occurs in all newborn infants by 48-72 hr after birth, with a gradual return to birth levels by 7-10 days of age. This transient deficiency of vitamin K—dependent factors is probably caused by lack of free vitamin K from the mother and absence of the bacterial intestinal flora normally responsible for the synthesis of vitamin K. Rarely in term infants, and more frequently in premature infants, accentuation and prolongation of this deficiency between the 2nd and 7th days of life result in spontaneous and prolonged bleeding. Breast milk is a poor source of vitamin K, but hemorrhagic complications are more frequent in breastfed than in formula-fed infants. This classic form of hemorrhagic disease of the newborn, which is responsive to and prevented by vitamin K therapy, must be distinguished from disseminated intravascular coagulopathy and from the more infrequent congenital deficiencies of one or more of the other factors that are unresponsive to vitamin K (see Chapter 476). Early-onset life-threatening vitamin K deficiency-induced bleeding (onset from birth to 24 hr) also occurs if the mother has been treated with drugs (phenobarbital, phenytoin) that interfere with vitamin K function. Late onset (>2 wk) is often associated with vitamin K malabsorption, as noted in neonatal hepatitis or biliary atresia (Table 103-5).

Hemorrhagic disease of the newborn resulting from severe transient deficiencies in vitamin K—dependent factors is characterized by bleeding that tends to be gastrointestinal, nasal, subgaleal, intracranial, or post-circumcision. Prodromal or warning signs (mild bleeding) may occur before serious intracranial hemorrhage. The prothrombin time, blood coagulation time, and partial thromboplastin time are prolonged, and levels of prothrombin (II) and factors VII, IX, and X are decreased. Vitamin K facilitates posttranscriptional carboxylation of factors II, VII, IX, and X. In the absence of carboxylation, such factors form PIVKA (proteins induced in vitamin K absence), which is a sensitive marker for vitamin K status. Bleeding time, fibrinogen, factors V and VIII, platelets, capillary fragility, and clot retraction are normal for maturity.

Intramuscular administration of 1 mg of vitamin K at the time of birth prevents the decrease in vitamin K—dependent factors in full-term infants, but it is not uniformly effective in the prophylaxis of hemorrhagic disease of the newborn, particularly in breastfed and in
Bibliography
premature infants. The disease may be effectively treated with a slow intravenous infusion of 1-5 mg of vitamin K₁, with improvement in coagulation defects and cessation of bleeding noted within a few hours. Serious bleeding, particularly in premature infants or those with liver disease, may require a transfusion of fresh-frozen plasma or whole blood. The mortality rate is low in treated patients.

A particularly severe form of deficiency of vitamin K–dependent coagulation factors has been reported in infants born to mothers receiving anticonvulsive medications (phenobarbital and phenytoin) during pregnancy. The infants may have severe bleeding, with onset within the first 24 hr of life; the bleeding is usually corrected by vitamin K₁, although in some the response is poor or delayed. A prothrombin time should be measured in cord blood, and the infant given 1-2 mg of vitamin K intravenously. If the prothrombin time is greatly prolonged and fails to improve, 10 mL/kg of fresh-frozen plasma should be administered.

The routine use of intramuscular vitamin K for prophylaxis in the United States is safe and is not associated with an increased risk of childhood cancer or leukemia. Although oral vitamin K (birth, discharge, 3-4 wk: 1-2 mg) has been suggested as an alternative, oral vitamin K is less effective in preventing the late onset of bleeding due to vitamin K deficiency and thus cannot be recommended for routine therapy. The intramuscular route remains the method of choice.

Other forms of bleeding may be clinically indistinguishable from hemorrhagic disease of the newborn responsive to vitamin K, but they are neither prevented nor successfully treated with vitamin K. A clinical pattern identical to that of hemorrhagic disease of the newborn may also result from any of the congenital defects in blood coagulation (see Chapters 476 and 477). Hematomas, melena, and postcircumcision and umbilical cord bleeding may be present; only 5-35% of cases of factor VIII and IX deficiency become clinically apparent in the newborn period. Treatment of the rare congenital deficiencies of coagulation factors requires fresh-frozen plasma or specific factor replacement.

**Disseminated intravascular coagulopathy** in newborn infants results in consumption of coagulation factors and bleeding. Affected infants are often premature; the clinical course is frequently characterized by asphyxia, hypoxia, acidosis, shock, hemangiomas, or infection. Treatment is directed at correcting the primary clinical problem, such as infection, interrupting consumption of clotting factors, and replacing them (see Chapter 483).

Infants with central nervous system or other bleeding posing an immediate threat to life should receive fresh-frozen plasma, vitamin K₁, and blood if needed as soon as possible after a blood specimen has been obtained for coagulation studies, which should include a determination of the number of platelets.

**The swallowed blood syndrome,** in which blood or bloody stools are passed, usually on the 2nd or 3rd day of life, may be confused with hemorrhage from the gastrointestinal tract. The blood may be swallowed during delivery or from a fissure in the mother’s nipple. Differentiation from gastrointestinal hemorrhage is based on the fact that the infant’s blood contains mostly fetal hemoglobin, which is alkali-resistant, whereas swallowed blood from a maternal source contains adult hemoglobin, which is promptly changed to alkaline hematin after the addition of alkali. Apt devised the following test for this differentiation: (1) Rinse a blood-stained diaper or some grossly bloody (red) stool with a suitable amount of water to obtain a distinctly pink supernatant hemoglobin solution; (2) centrifuge the mixture and decant the supernatant solution; (3) add 1 part of 0.25 N (1%) sodium hydroxide to 5 parts of the supernatant fluid. Within 1-2 min, a color reaction takes place: A yellow-brown color indicates that the blood is maternal in origin; a persistent pink indicates that it is from the infant. A control test with known adult or infant blood, or both, is advisable.

Widespread subcutaneous ecchymoses in premature infants at or immediately after birth are apparently a result of fragile superficial blood vessels rather than a coagulation defect. Administering vitamin K₁ to the mother during labor has no effect on the incidence of ecchymoses. Occasionally, an infant is born with petechiae or a generalized bluish suffusion limited to the face, head, and neck, probably as a result of venous obstruction by a nuchal cord or sudden increases in intrathoracic pressure during delivery. It may take 2-3 wk for such suffusions to disappear.

**NEONATAL THROMBOCYTOPENIC PURPURA**

See Chapter 484.

*Bibliography is available at Expert Consult.*


Chapter 104
Genitourinary System
Waldemar A. Carlo and Namasivayam Ambalavanan

See also Part XXIV.

Urinary tract anomalies (hydronephrosis, dysplasia, agenesis, cystic or solitary kidney) can often be identified by prenatal ultrasonography (see Table 96-1). After birth, the presence/extent of anomalies needs to be confirmed and followed by detailed evaluation and appropriate management. Multicystic and polycystic forms of kidney disease have high risk for mortality and renal morbidity. In contrast, the majority of mild dilatations have no clinical consequences but cause unnecessary anxiety in many cases.

One or both kidneys are often easily palpable in a newborn infant. When both are palpable and similar, infants usually do not have any particular diagnostic problems, but when only one kidney can be felt, a frequent impression is that it is larger than normal or is displaced by an intrinsic or extrinsic mass. Fetal lobulation may contribute to this impression. The problem usually resolves as the kidney becomes progressively less easily palpable during the early months of life. Because palpable enlargement or displacement of a kidney in a newborn may be due to hydronephrosis, neuroblastoma, mesoblastic nephroma, adrenal hemorrhage, or a cystic malformation, ultrasound examination is indicated.

RENAL VEIN THROMBOSIS
See Chapter 519.7.

Circumcision
Male circumcision is an elective procedure currently performed in many countries and in some religious and cultural groups. In the United States, the rate of male circumcision varies between 50% and 75% among various populations but has been declining recently. The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists have endorsed a policy statement in support of circumcision because of the health benefits.

The health benefits of circumcision include reduced acquisition and/or transmission of several sexually transmitted diseases (human immunodeficiency virus, human papillomavirus, herpes simplex virus type 2, and syphilis), possible prevention of urinary tract infections, and penile cancer. There is fair evidence that there are no significant differences in sexual function between circumcised and uncircumcised males. Even though the benefits of circumcision outweigh the rare but important complications (amputation of the penis or glans, infection), the health benefits are not large enough to recommend circumcision of all male infants. With appropriate counseling, parents can make a decision on what they think is the best interest of their baby in the context of their medical, ethical, religious, and cultural beliefs (see also Chapter 544).

Male circumcision entails the surgical removal of some of the foreskin (prepuce) of the penis. The surgery is performed under penile
nerve block anesthesia and under sterile conditions. The surgery includes dilation of the preputial orifice to visualize the glans, freeing the preputial epithelium from the epithelium of the glans, placement of the circumcision device (Gomco clamp, Plastibell, or Mogen clamp) to enhance hemostasis, and removal of foreskin.

Parents should be instructed on the care of the penis. The circumcised penis should be washed gently. A gauze with petroleum jelly can be used to cover the glans until the glans heals. The uncircumcised penis should be washed with soap and water on the outside. At birth, the foreskin is attached to the glans and cannot be retracted. The foreskin will separate naturally over several months. After separation, the foreskin is pulled back and the penis and inside of the foreskin can be washed with soap and water. After cleaning, the foreskin should be pulled back over the glans.

Bibliography is available at Expert Consult.
Bibliography

The Umbilicus

Waldemar A. Carlo and Namasivayam Ambalavanan

UMBILICAL CORD

The umbilical cord contains the 2 umbilical arteries, the umbilical vein, the rudimentary allantois, the remnant of the omphalomesenteric duct, and a gelatinous substance called Wharton jelly. The sheath of the umbilical cord is derived from the amnion. The muscular umbilical arteries contract readily, but the vein does not. The vein retains a fairly large lumen after birth. The normal cord at term is 55 cm long on average. Abnormally short cords are associated with antepartum abnormalities, including fetal hypotonia, oligohydramnios, and uterine constraint, and with increased risk for complications of labor and delivery for both mother and infant. Long cords (>70 cm) increase risk for true knots, wrapping around fetal parts (neck, arm), and/or prolapse. Straight untwisted cords are associated with fetal distress, anomalies, and intrauterine fetal demise.

When the cord sloughs after birth, portions of these structures remain in the base. The blood vessels are functionally closed but anatomically patent for 10-20 days. The arteries become the lateral umbilical ligaments; the vein, the ligamentum teres; and the ductus venosus, the ligamentum venosum. During this interval, the umbilical vessels are potential portals of entry for infection. The umbilical cord usually sloughs within 2 wk. Delayed separation of the cord, after more than 1 mo, has been associated with neutrophil chemotactic defects and overwhelming bacterial infection (see Chapter 130).

A single umbilical artery is present in approximately 5-10/1,000 births; the frequency is approximately 35-70/1,000 in twin births. Approximately 30% of infants with a single umbilical artery have congenital abnormalities, usually more than one; many such infants are stillborn or die shortly after birth. Trisomy 18 is one of the more frequent abnormalities. Because abnormalities may not be apparent on physical examination, it is important that at every delivery, the cut cord and the maternal and fetal surfaces of the placenta be inspected. The number of arteries present is an aid to the early suspicion and identification of abnormalities in the infants. For infants with a single umbilical artery but no other anomalies, the need for renal ultrasonography is controversial.

Patency of the omphalomesenteric (vitelline) duct may be responsible for intestinal obstruction, intestinal fistula with fecal or bilious draining, prolapse of the bowel, a polyp (cyst), or a Meckel diverticulum (see Chapter 331.2). Therapy is surgical excision of the anomaly.

A persistent urachus (urachal cyst, sinus, patent urachus, or diverticulum) is a result of failure of closure of the allantoic duct and is associated with bladder outlet obstruction. Patency should be suspected if a clear, light yellow, urine-like fluid is being discharged from the umbilicus. Symptoms include drainage, a mass or cyst, abdominal pain, local erythema, and infection. Urachal anomalies should be investigated by ultrasonography and a cystogram. Therapy is surgical excision of the anomaly and correction of any bladder outlet obstruction if present.

CONGENITAL OMPHALOCELE

An omphalocele is a herniation or protrusion of the abdominal contents into the base of the umbilical cord (Figs. 105-1 and 105-2). In contrast to the more common umbilical hernia, the sac is covered with peritoneum without overlying skin. The size of the sac that lies outside the abdominal cavity depends on its contents. Herniation of intestines into the cord occurs in approximately 1/5,000 births, and herniation of liver and intestines in 1/10,000 births. The abdominal cavity is

Figure 105-1 Small intact sac at the base of the umbilical cord. (From Clark DA, Thompson JE, Barnemeyer BM: Atlas of neonatology, ed 7, Philadelphia, 2000, WB Saunders.)

Figure 105-2 Intact sac with healthy organs visible. (From Clark DA, Thompson JE, Barnemeyer BM: Atlas of neonatology, ed 7, Philadelphia, 2000, WB Saunders.)
The general manifestations may be minimal and, if fasciitis has ruptured or if excessive mobilization of the skin would be necessary to cover the mass and its intact sac. The majority (>75%) of infants with omphalocele have associated congenital anomalies/syndromes, including Beckwith-Wiedemann syndrome (omphalocele, macrosomia, hypoglycemia), and other chromosomal (29%, including trisomies 13 and 18) and nonchromosomal (45%) multiple and isolated congenital anomalies (musculoskeletal, 24%; urogenital, 20%; cardiovascular, 15%; and central nervous system, 9%). The survival rate is approximately 80% overall, but in infants with isolated omphalocele, the survival rate is >90%.

**TUMORS**

Tumors of the umbilicus are rare and include angioma, enterotermatoma, dermoid cyst, myxosarcoma, and cysts of urachal or omphalomesenteric duct remnants.

**HEMORRHAGE**

Hemorrhage from the umbilical cord may be the result of trauma, inadequate ligation of the cord, or failure of normal thrombus formation. It may also indicate hemorrhagic disease of the newborn or other coagulopathies (especially factor XIII deficiency), septicemia, or local infection. The infant should be observed frequently during the first few days of life so that if hemorrhage does occur, it will be detected promptly.

**GRANULOMA**

The umbilical cord usually dries and separates within 6-8 days after birth. The raw surface becomes covered by a thin layer of skin; scar tissue forms, and the wound is usually healed within 12-15 days. The presence of saprophytic organisms delays separation of the cord and increases the possibility of invasion by pathogenic organisms. Mild infection or incomplete epithelialization may result in a moist granulating area at the base of the cord with a slight mucoid or mucopurulent discharge. Good results are usually obtained by cleansing with alcohol several times daily.

Persistence of granulation tissue at the base of the umbilicus is common. The tissue is soft, 3-10 mm in size, vascular and granular, and dull red or pink, and it may have a seropurulent secretion. Treatment is cauterization with silver nitrate, repeated at intervals of several days until the base is dry.

Umbilical granuloma must be differentiated from umbilical polyp, a rare anomaly resulting from persistence of all or part of the omphalomesenteric duct or the urachus. The tissue of the polyp is firm and resistant, is bright red, and has a mucoid secretion. If the polyp is communicating with the ileum or bladder, small amounts of fecal material or urine may be discharged intermittently. Histologically, the polyp consists of intestinal or urinary tract mucosa. Treatment is surgical excision of the entire omphalomesenteric or urachal remnant.

**INFECTIONS**

Although aseptic delivery and routine cord care (application of triple dye and other antiseptics to the umbilical stump and surrounding skin) decrease bacterial colonization and umbilical infection, the necrotic tissue of the umbilical cord is an excellent medium for bacterial growth. In a meta-analysis, triple dye was found to be more effective than alcohol in reducing omphalitis. Soap and water or dry care is not as effective in the prevention of omphalitis. Topical application of 4% chlorhexidine to the umbilical cord reduces neonatal mortality and omphalitis in community and primary care settings in developing countries. Omphalitis may remain localized or may spread to the abdominal wall, the peritoneum, the umbilical or portal vessels, or the liver. Infants with abdominal wall cellulitis or those with necrotizing fasciitis have a high incidence of associated bacteremia. Portal vein phlebitis may develop and result in the later onset of extrahepatic portal hypertension. The general manifestations may be minimal (periumbilical erythema), even when septicemia or hepatitis has resulted. Treatment includes prompt antibiotic therapy (with agents effective against *Staphylococcus aureus* and *Escherichia coli*) and, if abscess formation has occurred, surgical incision and drainage. Necrotizing fasciitis is often polymicrobial and has a high mortality.

**UMBILICAL HERNIA**

Often associated with diastasis recti, an umbilical hernia is due to imperfect closure or weakness of the umbilical ring. Predisposing factors include black race and low birthweight. The hernia appears as a soft swelling covered by skin that protrudes during crying, coughing, or straining and can be reduced easily through the fibrous ring at the umbilicus. The hernia consists of omentum or portions of the small intestine. The size of the defect varies from <1 cm in diameter to as much as 5 cm, but large defects are rare. Most umbilical hernias that appear before the age of 6 mo disappear spontaneously by 1 yr of age. Even large hernias (5-6 cm in all dimensions) have been known to disappear spontaneously by 5-6 yr of age. Strangulation is extremely rare. It is generally agreed that “strapping” is ineffective. Surgery is not advised unless the hernia persists to the age of 4-5 yr, causes symptoms, becomes strangulated, or becomes progressively larger after the age of 1-2 yr. Defects exceeding 2 cm are less likely to close spontaneously.

*Bibliography is available at Expert Consult.*
**Bibliography**


HYPERTHERMIA IN THE NEWBORN

Elevations in temperature (38-39°C [100-103°F]) are occasionally noted on the 2nd or 3rd day after birth in infants whose clinical course has been otherwise satisfactory. This disturbance is especially likely to occur in breastfed infants whose intake of fluid has been particularly low or in infants who are overdressed or are exposed to high environmental temperatures, either in an incubator, in a bassinette near a radiator, or in the sun.

The infant may lose weight. A consistent relationship may not be seen between the fever and the extent of weight loss or inadequacy of fluid intake. Urinary output and the frequency of voiding diminish. The fontanel may be depressed. The infant takes fluids avidly, and the apparent vigor of the infant is not consistent with the usual appearance of “being sick” from an infection. The rise in temperature may be associated with increases in serum levels of protein and sodium and in hematocrit. The possibility of local or systemic infection should be evaluated. Lowering the environmental temperature leads to prompt reduction of the fever and alleviation of symptoms. Oral hydration should be accomplished with additional breast milk or formula feeding and not with water, because of the risk of hyponatremia.

A more severe form of neonatal hyperthermia occurs in both newborn and older infants when they are warmly dressed. The diminished sweating capacity of newborn infants is a contributing factor. Warmly dressed infants left near stoves or radiators, traveling in well-heated automobiles, or left with bright sunlight shining directly on them through the windows of a closed room or automobile are likely to be victims. Body temperature may become as high as 41-44°C (106-111°F). The skin is hot and dry, and initially the infant usually appears
flushed and apathetic. The extremities are warm. Tachypnea and irritability may be noted. This stage may be followed by stupor, grayish pallor, coma, and convulsions. Hypernatremia may contribute to the convulsions. Mortality and morbidity (brain damage) rates are high. Hyperthermia has been associated with sudden infant death, and hemor rhagic shock and encephalopathy syndrome (see Chapter 70).

The condition is prevented by dressing infants in clothing suitable for the temperature of the immediate environment. In newborn infants, exposure of the body to usual room temperature or immersion in tepid water usually suffices to bring the temperature back to normal levels. Older infants may require cooling for a longer time by repeated immersion. Attention to possible fluid and electrolyte disturbance is essential.

Hyperthermia a few days after birth can result from infection, particularly herpes sepsis. Infants with infection appear ill with cold extremities, in contrast to the warm extremities of those in whom hyperthermia is from environmental causes.

NEONATAL COLD INJURY
Neonatal cold injury usually occurs in abandoned infants, infants in inadequately heated homes during cold spells when the outside temperature is low, and in preterm infants (see Chapter 76). The initial features are apathy, refusal of food, oliguria, and coldness to touch. The body temperature is usually between 29.5 and 35°C (85 and 95°F), and immobility, edema, and redness of the extremities, especially the hands and feet, and of the face are observed. Bradycardia and apnea may also occur. The facial erythema frequently gives a false impression of health and delays recognition that the infant is ill. Local hardening over areas of edema may lead to confusion with scleredema. Hypoglycemia and acidosis are common. Hemorrhagic manifestations are frequent; massive pulmonary hemorrhage is a common finding at autopsy.

Hyperthermia in preterm infants can be prevented with special plastic wraps that reduce evaporation and heat loss. Because of their high ratio of surface area to body mass, preterm infants are very vulnerable to evaporation heat loss. Infants at <28-30 wk of gestation should be placed inside a clear polyethylene bag without prior drying at birth. Neonatal cold injury occurs in even late preterm infants in low-resource settings and can be prevented with skin-to-skin (kangaroo mother) care and polyethylene plastic wraps. Treatment consists of warming and paying scrupulous attention to recognition and correction of hypotension and metabolic imbalances, particularly hypoglycemia. Prevention consists of providing adequate environmental heat. The mortality rate is approximately 10%; approximately 10% of survivors have evidence of brain damage.

EDEMA
Generalized edema occurs in association with hydrops fetalis (see Chapter 103.2) and in the offspring of diabetic mothers. In preterm infants, edema is often a consequence of a decreased ability to excrete water or sodium, although some have considerable edema without identifiable cause. Infants with respiratory distress syndrome may become edematous without heart failure. Edema of the face and scalp may be caused by pressure from the umbilical cord around the neck, and transient localized swelling of the hands or feet may similarly be caused by intrauterine pressure. Edema may be associated with heart failure. A lag in renal excretion of electrolytes and water may result in edema after a sudden large increase in intake of electrolytes, particularly with feeding of concentrated cow’s milk formulas. Rarely, idiopathic hypoproteinemia with edema lasting weeks or months is observed in term infants. The cause is unclear, and the disturbance is benign. Persistent edema of 1 or more extremities may represent congenital lymphedema (Milroy disease) or, in females, Turner syndrome. Generalized edema with hypoproteinemia may be seen in the neonatal period with congenital nephrosis and rarely with Hurler syndrome or after feeding hypoallergenic formulas to infants with cystic fibrosis of the pancreas. Chapter 647 describes sclerema.

HYPOCALCEMIA (TETANY)
See also Chapter 51.

Metabolic Bone Disease
Metabolic bone disease is a common complication in preterm infants. The smallest, sickest infants are at greatest risk. Progressive osteopenia with demineralized bones and, occasionally, pathologic fractures may develop. The major cause is inadequate intake of calcium and phosphorus to meet the requirements for growth. Poor intake of vitamin D is an additional risk factor. Contributing factors include prolonged parenteral nutrition, vitamin D and calcium malabsorption, intake of unsupplemented human milk, immobilization, and urinary calcium losses from long-term diuretic use. The serum alkaline phosphatase level is used to monitor metabolic bone disease and can be >1,000 units/L in severe cases. Fortified human milk and formulas designed for preterm infants provide higher amounts of calcium, phosphorus, and vitamin D; promote bone mineralization; and reduce metabolic bone disease. Treatment of fractures requires immobilization and administration of calcium, phosphorus, and, if needed, vitamin D (not more than 1,000 IU/day unless severe cholestasis or vitamin D resistance is present). See also Chapters 51 and 570.

Hypomagnesemia
Rarely, hypomagnesemia of unknown cause may occur in newborn infants, usually in association with hypocalcemia. It may also be associated with insufficient stores of skeletal magnesium secondary to deficient placental transfer, decreased intestinal absorption, neonatal hypoparathyroidism, hyperphosphatemia, renal loss (primary or secondary to drugs, e.g., amphotericin B), a defect in magnesium and calcium homeostasis, or iatrogenic deficiency caused by loss incurred during exchange transfusion or insufficient replacement during total intravenous alimentation. Infants of diabetic mothers may have lower than normal serum magnesium levels. The clinical manifestations of hypomagnesemia are indistinguishable from those of hypocalcemia and tetany and may, in fact, contribute to the accompanying hypocalcemia.

Hypomagnesemia occurs when serum magnesium levels fall below 1.5 mg/dL (0.62 mmol/L), although clinical signs do not usually develop until serum magnesium levels fall below 1.2 mg/dL. During exchange transfusion with citrated blood, which is low in magnesium because of binding by citrate, serum magnesium decreases about 0.5 mg/dL (0.2 mmol/L); approximately 10 days are required for return to normal. In noniatrogenic hypomagnesemia, the serum magnesium level may be <0.5 mg/dL. Serum calcium in either instance is usually at levels noted in hypocalcemic tetany, but the serum phosphorus value is normal or high. Because the hypocalcemia accompanying hypomagnesemia is inadequately corrected by administration of calcium alone, hypomagnesemia should also be suspected in any patient with tetany not responding to calcium therapy.

Immediate treatment consists of intramuscular injection of magnesium sulfate. For newborn infants, 25-50 mg/kg/dose every 8 hr for 3-4 doses usually suffices. The accompanying hypocalcemia usually corrects itself as the hypomagnesemia resolves. The same daily dose can be given for oral maintenance therapy. Four to 5 times higher doses may be required in malabsorptive states. In most cases, the metabolic defect is transient, and treatment can be discontinued after 1-2 wk. A few patients appear to have a permanent form of the disease that requires continuous oral supplementation with magnesium to prevent recurrence of hypomagnesemia. No residual damage to the central nervous system is evident after prompt treatment.

HYPERMAGNESEMA
Hypermagnesemia may occur in newborn infants of mothers treated with magnesium sulfate during labor. At high serum levels, the central nervous system is depressed and infants have respiratory depression that may require mechanical ventilation. Lower levels may result in hypoventilation, lethargy, flaccidity, hyporeflexia, and poor sucking. Hypermagnesemia may be associated with failure to pass meconium. The upper limit of normal magnesium is 2.8 mg/dL (1.15 mmol/L), but serious symptoms rarely occur at levels <5 mg/dL (2.1 mmol/L). In most cases, no specific therapy (beyond supportive care and maintenance of respiratory support) is required. Intravenous calcium and
SUBSTANCE ABUSE AND NEONATAL ABSTINENCE (WITHDRAWAL)

Substance abuse during pregnancy can be a serious problem for both the mother and her newborn. The mother may suffer adverse consequences of her addiction, including episodes of drug withdrawal during pregnancy and illnesses related to high-risk behavior. Effects on the fetus and newborn include chronic or intermittent drug exposure, poor maternal nutrition, acute withdrawal shortly after birth, and long-term effects on physical growth and neurodevelopment. Because infants with in utero drug exposure often have social and environmental risk factors and may have been exposed to multiple substances, it may be difficult to evaluate the effects of specific in utero drug exposure on long-term neurodevelopmental outcome.

Pregnancies in women who use illegal drugs or alcohol are high risk. Prenatal care is usually inadequate, and these women have a higher incidence of sexually transmitted infections, including syphilis, HIV, and hepatitis. In addition, the risk of preterm labor, intrauterine growth restriction, premature rupture of membranes, and perinatal morbidity and mortality is higher. Physiologic addiction to narcotics occurs in most infants born to actively addicted mothers because opiates cross the placenta. Withdrawal may manifest even before birth as increased activity of the fetus when the mother feels a need for the drug or withdrawal symptoms develop. The clinical syndrome associated with opioid withdrawal has been termed the neonatal abstinence syndrome. Withdrawal signs develop during the 1st wk after birth in 55-94% of newborn infants exposed to opioids in utero. Neonatal withdrawal signs have also been described in infants exposed antenatally to benzodiazepines, barbiturates, alcohol, and other drugs. Heroin addiction results in a 50% incidence of low birthweight infants, half of whom are small for gestational age. Chronic infections, maternal undernutrition, and a direct fetal growth–inhibiting effect are possible causes. The rate of stillbirths increases, but not the incidence of congenital anomalies. Clinical manifestations of withdrawal occur in 50-75% of infants, usually beginning within the 1st 48 hr, depending on the daily maternal dose (<6 mg/24 hr is associated with no or mild symptoms), the duration of addiction (duration >1 yr has a >70% incidence of withdrawal), and the time of the last maternal dose (the incidence is higher if the last dose was taken within 24 hr of birth). Rarely, symptoms may appear as late as 4-6 wk of age. The incidence of respiratory distress syndrome and hyperbilirubinemia may be decreased in preterm infants of heroin users; accelerated production of respiratory distress syndrome and hyperbilirubinemia may be associated with opioid withdrawal.

Tremors and hyperirritability are the most prominent symptoms. The tremors may be fine or jittery and indistinguishable from those of hypoglycemia, but they are more often coarse, “flapping,” and bilateral; the limbs are frequently rigid, hyperreflexic, and resistant to flexion and extension. Irritability and hyperactivity are generally marked and may lead to skin abrasions. Other signs include wakefulness, hyperacusis, hypertonicity, tachypnea, diarrhea, vomiting, high-pitched cry, fist sucking, poor feeding with weight loss (disorganized sucking), and fever. Sneezing, yawning, hiccuping, myoclonic jerks, convulsions, abnormal sleep cycles, nasal stuffiness, apnea, flushing alternating rapidly with pallor, and lacrimation are less common. The Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS) is a useful way to evaluate neonates exposed to opiates or other drugs (Table 106-1). The risk of sudden infant death syndrome is higher in such neonates. The diagnosis is generally established from the history and clinical findings. Examining the urine for opiates may reveal only low levels during withdrawal, but quinine, which is often mixed with heroin, may be present in higher concentrations. Meconium testing is more accurate than neonatal urine drug testing. Hypoglycemia and hypocalcemia should be excluded.

Methadone treatment of the mother is associated with severe withdrawal symptoms, the incidence varying from 20-90%. Mothers taking methadone usually have better prenatal care than those taking heroin; these mothers have a high incidence of polysubstance abuse, including alcohol, barbiturates, and tranquilizers, and they are often heavy smokers. The incidence of congenital anomalies is not increased. The average birthweight of infants of mothers taking methadone is higher than that of infants of heroin-addicted mothers; the clinical manifestations are similar, except that the former group has a higher incidence of seizures (10-20%) and later onset (2-6 wk of age) of withdrawal. Women who continue to abuse heroin, even if they enter a methadone program, are more likely to have preterm and/or low birthweight infants than those born to women who stop using heroin. They are also more likely to suffer withdrawal and have a higher risk of neonatal mortality.

### Table 106-1 Neurobehavioral Scale

<table>
<thead>
<tr>
<th>DOMAIN</th>
<th>ITEMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiologic</td>
<td>Labored breathing</td>
</tr>
<tr>
<td></td>
<td>Nasal flaring</td>
</tr>
<tr>
<td>Autonomic</td>
<td>Sweating</td>
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<tr>
<td></td>
<td>Spit-up</td>
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<tr>
<td></td>
<td>Hiccoughing</td>
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<tr>
<td></td>
<td>Sneezing</td>
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<tr>
<td></td>
<td>Nasal stuffiness</td>
</tr>
<tr>
<td></td>
<td>Yawning</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Abnormal sucking</td>
</tr>
<tr>
<td></td>
<td>Choreiform movements</td>
</tr>
<tr>
<td></td>
<td>Athetoid postures and movements</td>
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<tr>
<td></td>
<td>Tremors</td>
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<td></td>
<td>Cogwheel movements</td>
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<tr>
<td></td>
<td>Startles</td>
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<tr>
<td></td>
<td>Hypertonia</td>
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<tr>
<td></td>
<td>Back arching</td>
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<tr>
<td></td>
<td>Fisting</td>
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<tr>
<td></td>
<td>Cortical thumb</td>
</tr>
<tr>
<td></td>
<td>Myoclonic jerks</td>
</tr>
<tr>
<td></td>
<td>Generalized seizures</td>
</tr>
<tr>
<td></td>
<td>Abnormal posture</td>
</tr>
<tr>
<td>Skin</td>
<td>Pallor</td>
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<tr>
<td></td>
<td>Mottling</td>
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<tr>
<td></td>
<td>Lividity</td>
</tr>
<tr>
<td></td>
<td>Overall cyanosis</td>
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<td></td>
<td>Circumoral cyanosis</td>
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<tr>
<td></td>
<td>Periocular cyanosis</td>
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<tr>
<td>Visual</td>
<td>Gaze aversion during orientation</td>
</tr>
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<td></td>
<td>Pull-down during orientation</td>
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<tr>
<td></td>
<td>Fuss/cry during orientation</td>
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<td></td>
<td>Obligatory following during orientation</td>
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<td></td>
<td>End-point nystagmus</td>
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<td></td>
<td>Sustained spontaneous nystagmus</td>
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<td></td>
<td>Visual locking</td>
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<td></td>
<td>Hyperalertness</td>
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<tr>
<td></td>
<td>Setting sun sign</td>
</tr>
<tr>
<td></td>
<td>Roving eye movements</td>
</tr>
<tr>
<td></td>
<td>Strabismus</td>
</tr>
<tr>
<td></td>
<td>Tight blinking</td>
</tr>
<tr>
<td></td>
<td>Other abnormal eye signs</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Gagging/choking</td>
</tr>
<tr>
<td></td>
<td>Loose stools, watery stools</td>
</tr>
<tr>
<td></td>
<td>Excessive gas, bowel sounds</td>
</tr>
<tr>
<td>State</td>
<td>High-pitched cry</td>
</tr>
<tr>
<td></td>
<td>Monotone-pitch cry</td>
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<tr>
<td></td>
<td>Weak cry</td>
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<tr>
<td></td>
<td>No cry</td>
</tr>
<tr>
<td></td>
<td>Extreme irritability</td>
</tr>
<tr>
<td></td>
<td>Ablupt state changes</td>
</tr>
<tr>
<td></td>
<td>Inability to achieve quiet awake state</td>
</tr>
</tbody>
</table>

**Table 106-2** Pharmacologic Therapy for Neonatal Abstinence Syndrome

<table>
<thead>
<tr>
<th>DRUG</th>
<th>INITIAL DOSING</th>
<th>DOZING INCREASES</th>
<th>RESCUE DOSING</th>
<th>ADD ADJUVANT THERAPY</th>
<th>WEANING SCHEDULE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>0.1 mg kg(^{-1}) dose(^{-1}) orally every 4 hr</td>
<td>Increase by 20–30% every 12 hr until scores &lt; 8 × 24 hr</td>
<td>Repeat previous dose between scheduled dose intervals</td>
<td>At morphine dose of 1.25 mg kg(^{-1}) dose(^{-1}), add phenobarbital or clonidine</td>
<td>Decrease by 10% every 24 hr, while scores &lt; 8. Discontinue when 0.15 mg kg(^{-1}) dose(^{-1})</td>
</tr>
<tr>
<td>Methadone</td>
<td>0.1 mg kg(^{-1}) dose(^{-1}) orally every 12 hr</td>
<td>Calculate entire methadone dose for previous 24 hr and divide by two for BID dosing</td>
<td>Additional dosing of 0.025 mg kg(^{-1}) dose(^{-1}) every 4 hr while scoring &gt; 8. Max dose 0.5 mg kg(^{-1}) dose(^{-1})</td>
<td>When max dosing has been reached</td>
<td>Decrease by 10% every 1-2 wk. Discontinue when 0.05 mg kg(^{-1}) dose(^{-1})</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>15.9 µg kg(^{-1}) dose(^{-1}) divided in 3 doses, orally</td>
<td>Increase by 25%</td>
<td>Max dose 60 µg kg(^{-1}) dose(^{-1})</td>
<td></td>
<td>After 3 days of stabilization, decrease by 10% while scores &lt; 8. Discontinue when dose is 10% of initial dose</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>20 mg/kg loading</td>
<td>Maintenance dose 5 mg/kg</td>
<td></td>
<td>Adjuvant</td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>0.5 to 1.5 µg/kg orally</td>
<td>Increase by over 1 to 2 days to target dose 3 to 5 µg kg(^{-1}) day(^{−1}), divided every 4–6 hr</td>
<td></td>
<td>Adjuvant</td>
<td>No taper required</td>
</tr>
</tbody>
</table>


**Buprenorphine** (a partial μ-opioid agonist) is a synthetic opioid often used for the treatment of opioid dependence, used either alone (Subutex) or in combination with naloxone (Suboxone). Although the incidence of neonatal symptoms after maternal treatment with methadone and buprenorphine may be similar, the pattern of symptoms may be different; more tremor and hyperactive Moro reflex with methadone and more nasal stuffiness, sneezing, and loose stools with buprenorphine. Infants born to mothers treated with buprenorphine develop abstinence symptoms 1-2 days later than those of mothers on methadone. Infants born to buprenorphine-treated mothers also require less postnatal morphine doses, have a shorter duration of treatment, and are discharged from the hospital approximately 5 days sooner than methadone-exposed infants.

**Alcohol withdrawal** is uncommon. Infants of women who have been drinking immediately before delivery may have alcohol on their breath for several hours because it rapidly crosses the placenta. Blood levels in the infant are similar to those in the mother. Hypoglycemia and metabolic acidosis may be present. Infants in whom withdrawal symptoms develop often become agitated and hyperactive, with marked tremors lasting 72 hr, followed by about 48 hr of lethargy before return to normal activity. Seizures may develop.

**Phenobarbital withdrawal** usually occurs in infants of mothers addicted to the drug. Symptoms begin at a median age of 7 days (range: 2-14 days). Infants may have a brief acute stage consisting of irritability, constant crying, sleeplessness, hiccuping, and moistening movements, followed by a subacute stage consisting of voracious appetite, frequent regurgitation and gagging, episodic irritability, hyperacusis, sweating, and a disturbed sleep pattern, all of which may last 2-4 mo.

**Cocaine abuse** in pregnant women is common, but withdrawal in their infants is unusual; the pregnancy may be complicated by premature labor, abruptio placenta, and fetal asphyxia. Infants may have intrauterine growth restriction and neurobehavioral deficits characterized by impaired state regulation, impaired auditory information processing, developmental delay, and learning disabilities. At 24 mo of age, they score lower on the mental portion of the Bayley Scales of Infant Development and are twice as likely to have developmental delay. Family disorganization, polysubstance abuse, sexually transmitted infections, and child abuse and neglect may also be present. At 4 yr of age, children exposed prenatally to cocaine demonstrate specific cognitive impairments (visual–spatial and math skills; general knowledge) and are less likely to have an IQ above the normative mean. With a more enriching home environment, IQ scores of cocaine-exposed children are similar to those of nonexposed children.

**Treatment**

The decision to use drug therapy for neonatal drug withdrawal should be based on the presence of signs of withdrawal. Infants with confirmed drug exposure who do not have signs of withdrawal do not require pharmacologic treatment. Drug withdrawal is a self-limiting process. However, withdrawal from sedative-hypnotic drugs or narcotics can be life-threatening. Indications for drug treatment include seizures, poor feeding, diarrhea, excessive vomiting, inability to sleep, and fever. Several methods to assess severity of the withdrawal are available.

Infants who are undergoing opiate withdrawal require care in a quiet environment with reduction of external stimuli and swaddling. Pharmacologic treatment of heroin and methadone withdrawal requires opiate replacement during the 1st wk or 2 of life (Table 106-2). Methadone is often the drug of choice, but oral or sublingual buprenorphine is an alternate approach. Adjunct treatment with phenobarbital or clonidine is rarely necessary. Methadone withdrawal may require larger amounts of medication for longer periods to control clinical manifestations than are needed for heroin withdrawal. The Modified Finnegan’s Neonatal Abstinence Scoring Tool, Lipsitz Neonatal Drug- Withdrawal Scoring System, or other semiojective scoring tools may be used by clinicians to evaluate withdrawal and help with decisions regarding initiation or adjustment of therapy. The dose and duration of therapy may be adjusted according to the clinical response. Parenteral administration of fluids may be necessary to prevent aspiration or dehydration until the symptoms are brought under control.

Mortality from withdrawal is <5% and may be negligible with early recognition and treatment. The prognosis for normal development is affected by the adverse circumstances of high-risk pregnancy and delivery and by the environment to which the infant is returned after recovery, as well as by the effects of the particular drug on fetal and subsequent neonatal development.

#### 106.1 Maternal Selective Serotonin Reuptake Inhibitors and Neonatal Behavioral Syndromes

**Waldemar A. Carlo**

Women of childbearing age have a combined incidence of depression and anxiety of approximately 19%. Selective serotonin reuptake inhibitors (SSRIs; fluoxetine, paroxetine, sertraline, citalopram, fluvoxamine) and, less often, serotonin norepinephrine reuptake inhibitors (venla-
Faxine, duloxetine) have been used to treat pregnant women with depression or anxiety disorders. Exposure to these agents during pregnancy may inconsistently produce congenital malformations (see Chapter 96). In addition, poor neonatal adaptation has been noted with the use of many of these agents, but most often with paroxetine and fluoxetine.

It is unclear whether poor neonatal adaptation is a result of serotonin overstimulation (serotonin syndrome) or withdrawal (serotonin discontinuation syndrome). Indeed, both conditions may occur with different agents. Paroxetine has a short half-life and few if any active metabolites, and is also a potent muscarinic blocking agent. Serum paroxetine levels after birth decline rapidly. Neonatal adaptive symptoms after late pregnancy exposure to paroxetine may be withdrawal with cholinergic overdrive. Symptoms may also be delayed. In contrast, fluoxetine and its active metabolite (nor-fluoxetine) have long half-lives and may produce a serotonin syndrome of acute toxicity. Onset may be at birth or in the 1st 24 hr of life. The cord blood level of fluoxetine is equal to blood level in the mother. All agents cross the placental and blood–brain barriers.

A neonatal behavioral syndrome that has features of both direct serotonin toxicity and withdrawal (cholinergic overdrive) is noted in Figure 106-1 and is characterized by central nervous system (irritability, excess or restless sleep), motor (agitation, tremor, hyperreflexia, rigidity, hypotonia or hypertonia), respiratory (nasal congestion, respiratory distress, tachypnea), gastrointestinal (diarrhea, emesis, poor feeding) and systemic (hypothermia or hyperthermia, hypoglycemia) manifestations. Most infants have only mild symptoms that resolve within 2 wk; a severe syndrome characterized by seizures, dehydration, weight loss, hyperpyrexia, and respiratory failure is present in 1%. No deaths have been reported.

**Treatment** is directed at the individual manifestations and accompanied by supportive therapies. A method of prevention of neonatal SSRI withdrawal has been proposed that consists of weaning the mother from the SSRI in the 3rd trimester of pregnancy. The advantages of this approach for the fetus must be weighed against the risk for the mother of recurrence of psychiatric symptoms during the last trimester and postpartum period.

### 106.2 Fetal Alcohol Syndrome

**Waldemar A. Carlo**

High levels of alcohol ingestion during pregnancy can be damaging to embryonic and fetal development. A specific pattern of malformation identified as fetal alcohol syndrome has been documented, and major and minor components of the syndrome are expressed in 1-2 infants/1,000 live births (Table 106-3). Both moderate and high levels of alcohol intake during early pregnancy may result in alterations in

#### Table 106-3 Fetal Alcohol Syndrome Surveillance Network Case Definition Categories

<table>
<thead>
<tr>
<th>Case Definition Category</th>
<th>Face</th>
<th>Central Nervous System</th>
<th>Growth</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confirmed FAS phenotype with or without maternal alcohol exposure</strong>*</td>
<td>Abnormal facial features consistent with FAS as reported by a physician or Two of the following: short palpebral fissures, abnormal philtrum, thin upper lip</td>
<td>Frontal-occipital circumference ≤10th percentile at birth or any age or Standardized measure of intellectual function ≤1 SD below the mean or Standardized measure of developmental delay ≤1 SD below the mean or Developmental delay or mental retardation diagnosed by a qualified examiner (e.g., psychologist or physician) or Attention deficit disorder diagnosed by a qualified evaluator</td>
<td>Intrauterine weight or height corrected for gestational age ≤10th percentile or Postnatal weight or height ≤10th percentile for age or Postnatal weight for height ≤10th percentile</td>
</tr>
<tr>
<td><strong>Probable FAS phenotype with or without maternal alcohol exposure</strong>*</td>
<td>Required; facial features same as above</td>
<td>Must meet either central nervous system or growth criteria as outlined above</td>
<td></td>
</tr>
</tbody>
</table>

*Documentation in the records of some level of maternal alcohol use during the index pregnancy.

FAS, fetal alcohol syndrome; SD, standard deviation.


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**Figure 106-1** Neonatal signs after late in utero exposure to serotonin reuptake inhibitors. Frequencies of specific signs reported to the U.S. Food and Drug Administration (FDA) Adverse Events Reporting System. Ordered by frequency of occurrence (n = 57 infants). EEG, electroencephalographic. (From Moses-Kolko EL, Bogen D, Perel J, et al: Neonatal signs after late in utero exposure to serotonin reuptake inhibitors, JAMA 293:2372–2383, 2005.)

**Table 106-3** Fetal Alcohol Syndrome Surveillance Network Case Definition Categories

**Case Definition Category**

- Confirmed FAS phenotype with or without maternal alcohol exposure
- Probable FAS phenotype with or without maternal alcohol exposure

**PHENOTYPE POSITIVE**

- Abnormal facial features consistent with FAS as reported by a physician
- Frontal-occipital circumference ≤10th percentile at birth or any age
- Intrauterine weight or height corrected for gestational age ≤10th percentile
- Required; facial features same as above
- Must meet either central nervous system or growth criteria as outlined above

**Face**

- Two of the following: short palpebral fissures, abnormal philtrum, thin upper lip
- Standardized measure of intellectual function ≤1 SD below the mean
- Postnatal weight or height ≤10th percentile for age
- Attention deficit disorder diagnosed by a qualified evaluator

**Central Nervous System**

- Frontal-occipital circumference ≤10th percentile at birth or any age
- Postnatal weight or height ≤10th percentile for age
- Developmental delay or mental retardation diagnosed by a qualified examiner (e.g., psychologist or physician)

**Growth**

- Intrauterine weight or height corrected for gestational age ≤10th percentile
- Attention deficit disorder diagnosed by a qualified evaluator
growth and morphogenesis of the fetus; the greater the intake, the more severe the signs. The risk of abnormality for infants born to heavy drinkers is twice that for infants born to moderate drinkers; in one study, 32% of infants born to heavy drinkers had congenital anomalies, compared with 9% of those born to abstinent mothers and 14% of those born to moderate drinkers. Additional maternal risk factors associated with fetal alcohol syndrome are advanced maternal age, low socioeconomic status, poor psychological indicators, and binge drinking.

Characteristics of fetal alcohol syndrome include (a) prenatal onset and persistence of growth deficiency for length, weight, and head circumference; (b) facial abnormalities, including short palpebral fissures, epicanthal folds, maxillary hypoplasia, micrognathia, smooth philtrum, and a thin, smooth upper lip (Fig. 106-2); (c) cardiac defects, primarily septal defects; (d) minor joint and limb abnormalities, including some restriction of movement and altered palmar crease patterns; and (e) delay of development and mental deficiency varying from borderline to severe (see Table 106-2). Fetal alcohol syndrome is a common identifiable cause of mental retardation. The severity of dysmorphogenesis may range from severely affected infants with full manifestations of fetal alcohol syndrome to those mildly affected with only a few manifestations.

The detrimental effects may be a consequence of the alcohol itself or to one of its breakdown products. Some evidence suggests that alcohol may impair placental transfer of essential amino acids and zinc, both of which are necessary for protein synthesis, an effect that may account for the intrauterine growth restriction.

Treatment of infants with fetal alcohol syndrome is difficult because no specific therapy exists. These infants may remain hypotonic and tremulous despite sedation, and the prognosis is poor. Counseling with regard to recurrence is important. Prevention is achieved by eliminating alcohol intake after conception.

*Figure 106-2* Characteristics of fetal alcohol syndrome. At birth (A) and at 4 yr of age (B). Note the short palpebral fissures; long, smooth philtrum with vermillion border; and hirsutism in the newborn. (From Jones KL, Smith DW: Recognition of the fetal alcohol syndrome in early infancy, Lancet 2:999–1001, 1973.)

*Bibliography is available at Expert Consult.*
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The endocrinopathies are discussed in detail in Part XXVI.

**Pituitary dwarfism** is not usually apparent at birth, although male infants with panhypopituitarism may have neonatal hypoglycemia, hyperbilirubinemia, and micropenis. Conversely, constitutional dwarfs usually have length and weight suggestive of prematurity when born after a normal gestational period; otherwise, their physical appearance is normal.

**Congenital hypothyroidism** is one of the most common preventable causes of mental retardation. Congenital screening followed by thyroid hormone replacement treatment started within 2 wk after birth can normalize cognitive development in children with congenital hypothyroidism. Congenital hypothyroidism occurs in approximately 1/4,000 births (see Chapter 565). Because most infants with congenital hypothyroidism are asymptomatic at birth, all states screen for it. Even though screening is standard in many countries, millions of infants born throughout the world are not screened for congenital hypothyroidism. Thyroid deficiency may also be apparent at birth in genetically determined cretinism or in infants of mothers treated with antithyroid medications or during a pregnancy complicated by maternal hyperthyroidism. Constipation, prolonged jaundice, goiter, lethargy, or poor peripheral circulation as shown by persistently mottled skin or cold extremities should suggest cretinism. Thyroid hormone treatment is aimed to maintain total thyroxine or free thyroxine in the upper half of the normal range during the 1st 3 yr after birth. Early diagnosis and treatment of congenital thyroid hormone deficiency improve intellectual outcome and are facilitated by screening of all newborn infants for this deficiency.
Transient hypothyroxinemia of prematurity is most common in ill and very premature infants. These infants have low thyroxine levels but normal levels of serum thyrotropin and other tests of the pituitary–hypothalamic axis indicating that they are probably chemically euthyroid. Trials of thyroid hormone replacement have reported no difference in developmental outcomes or other morbidities. Current practice is to follow thyroxine levels until they normalize. Transient hyperthyroidism may occur at birth in infants of mothers with hyperthyroidism or in infants whose mothers have been receiving thyroid medication.

Transient hypoparathyroidism may manifest as tetany of the newborn (see Chapter 571). The adrenal glands are subject to numerous disturbances, which may become apparent and require lifesaving treatment during the neonatal period. Acute adrenal hemorrhage and failure may occur after breech or other traumatic deliveries or in association with overwhelming infection. Signs of adrenal insufficiency and shock can occur. Congenital adrenal hyperplasia is suggested by vomiting, diarrhea, dehydration, hyperkalemia, hypotenremia, shock,ambiguous genitals, or clitoral enlargement. Some infants have ambiguous genitals and hypertension. Because the condition is genetically determined, newborn siblings of patients with the salt-losing variety of adenocortical hyperplasia should be closely observed for manifestations of adrenal insufficiency. Newborn screening and early diagnosis and therapy for this disorder may prevent severe salt wasting and adverse outcomes. Congenitally hypoplastic adrenal glands may also give rise to adrenal insufficiency during the 1st few wk of life.

Female infants with webbing of the neck, lymphangiectatic edema, hypoplasia of the nipples, cutis laxa, low hairline at the nape of the neck, low-set ears, high-arched palate, deformities of the nails, cubitus valgus, and other anomalies should be suspected of having gonadal dysgenesis.

Transient diabetes mellitus (see Chapter 589) is rare and is encountered only in newborns. It usually manifests as dehydration, loss of weight, or acidosis in infants who are small for gestational age.

Bibliography is available at Expert Consult.

107.1 Infants of Diabetic Mothers

Waldemar A. Carlo

Women with diabetes in pregnancy (type 1, type 2, and gestational) are at increased risk for adverse pregnancy outcomes. Adequate glycemic control before and during pregnancy is crucial to improving outcomes.

Diabetic mothers have a high incidence of polyhydramnios, preeclampsia, pyelonephritis, preterm labor, and chronic hypertension; their fetal mortality rate is greater than that of nondiabetic mothers, especially after 32 wk of gestation. Fetal loss throughout pregnancy is associated with poorly controlled maternal diabetes (especially ketoacidosis) and congenital anomalies. Most infants born to diabetic mothers are large for gestational age. If the diabetes is complicated by vascular disease, infants may be growth restricted, especially those born after 37 wk of gestation. The neonatal mortality rate is >5 times that of infants of nondiabetic mothers and is higher at all gestational ages and in every birthweight for gestational age category.

PATHOPHYSIOLOGY

The probable pathogenic sequence is that maternal hyperglycemia causes fetal hyperglycemia, and the fetal pancreatic response leads to fetal hyperinsulinemia; fetal hyperinsulinemia and hyperglycemia then cause increased hepatic glucose uptake and glycogen synthesis, accelerated lipogenesis, and augmented protein synthesis (Fig. 107-1). Related pathologic findings are hypertrophy and hyperplasia of the pancreatic islet β cells, increased weight of the placenta and infant organs except for the brain, myocardial hypertrophy, increased amount of cytoplasm in liver cells, and extramedullary hematopoiesis. Hyperinsulinism and hyperglycemia produce fetal acidosis, which may result in an increased rate of stillbirth. Separation of the placenta at birth suddenly interrupts glucose infusion into the neonate without a proportional effect on the hyperinsulinism, and hypoglycemia and attenuated lipolysis may develop during the 1st few hr after birth.

Hyperinsulinemia has been documented in infants of mothers with gestational diabetes and in those of mothers with insulin-dependent diabetes (diabetic mothers) without insulin antibodies. The former group also has significantly higher fasting plasma insulin levels than normal newborns do despite similar glucose levels; they also respond to glucose with an abnormally prompt elevation in plasma insulin and assimilate a glucose load more rapidly. After arginine administration, they also have an enhanced insulin response and increased disappearance rates of glucose in comparison with normal infants. In contrast, fasting glucose production and utilization rates are diminished in infants of mothers with gestational diabetes. The lower free fatty acid levels in infants of mothers with insulin-dependent diabetes reflect their hyperinsulinemia. With good prenatal diabetic control, the incidence of macrosomia and hypoglycemia has decreased.

Although hyperinsulinism is probably the main cause of hypoglycemia, the diminished epinephrine and glucagon responses that occur may be contributing factors. Congenital anomalies correlate with poor metabolic control during the periconception and organogenesis periods and may be the result of hyperglycemia-induced teratogenesis. Chronic fetal hypoxia, indicated by elevated amniotic fluid erythropoietin values, is associated with increased fetal and neonatal morbidity.

CLINICAL MANIFESTATIONS

Infants of mothers with diabetic and those of mothers with gestational diabetes often bear a surprising resemblance to each other (Fig. 107-2). They tend to be large and plump as a result of increased body fat and enlarged viscera, with puffy, p lethoric facies resembling that of patients who have been receiving corticosteroids. These infants may also,
Bibliography

gestational age rather than total body weight. In addition, these infants have an increased incidence of hyperbilirubinemia, polyhydramnios, and renal vein thrombosis; the last should be suspected in the infant with a flank mass, hematuria, and thrombocytopenia.

The incidence of congenital anomalies is increased 3-fold in infants of diabetic mothers; cardiac malformations (ventricular or atrial septal defect, transposition of the great vessels, truncus arteriosus, double-outlet right ventricle, tricuspid atresia, coarctation of the aorta) and lumbosacral agenesis are most common. Additional anomalies include neural tube defects, hydronephrosis, renal agenesis and dysplasia, duodenal or anorectal atresia, situs inversus, double ureter, and holoprosencephaly. These infants may also demonstrate abdominal distention caused by a transient delay in development of the left side of the colon, the small left colon syndrome.

**TREATMENT**

Prophylactic treatment of infants of diabetic mothers should be initiated before birth by means of preconception and frequent prenatal evaluations of all women with diabetes and pregnant women with gestational diabetes, evaluation of fetal maturity, biophysical profile, Doppler velocimetry, and planning of the delivery of these infants in hospitals where expert obstetric and pediatric care is continuously available. Periconception glucose control reduces the risk of anomalies and other adverse outcomes, and glucose control during labor reduces the incidence of neonatal hypoglycemia. Women with type 1 diabetes who have tight glucose control during pregnancy (average daily glucose levels <95 mg/dL) deliver infants with birthweights and anthropomorphic features similar to those of infants of nondiabetic mothers. Treatment of gestational diabetes also reduces complications; dietary advice, glucose monitoring, metformin, and insulin therapy as needed decrease the rate of serious perinatal outcomes (death, shoulder dystocia, bone fracture, or nerve palsy). Women with gestational diabetes may also be treated successfully with glyburide, which may not cross the placenta. In these mothers, the incidence of macrosomia and neonatal hypoglycemia is similar to that in mothers with insulin-treated gestational diabetes.

Regardless of size, infants of diabetic mothers should initially receive close observation and care (Fig. 107-3). Infants should initiate feedings within 1 hr after birth. A screen glucose test should be performed within 30 minutes of the first feed. Transient hypoglycemia is common during the 1st 2-3 hr after birth and may be part of normal adaptation to extraterine life. The target plasma glucose concentration is ≥45 mg/dL before feeds. Clinicians need to assess the overall metabolic and physiologic status, considering these in the management of hypoglycemia. According to a statement from the American Academy of Pediatrics, treatment is indicated if the plasma glucose is <40 mg/dL and clinical symptoms of hypoglycemia are present. In asymptomatic infants, treatment is indicated if the plasma glucose is <30 mg/dL. Feeding is the initial treatment for hypoglycemia. Gavage feeding with breast milk or formula can be given. Recurrent hypoglycemia can be treated with repeat feedings or intravenous glucose as needed. Infants with persistent glucose levels <25 mg/dL during the 1st 4 hr after birth and <35 mg/dL during 4-24 hr after birth should be treated with intravenous glucose. A dose of 200 mg/kg of dextrose (2 mL/kg of 10% dextrose) should be administered to infants with plasma glucose below these limits. If question arises about an infant’s ability to tolerate oral feeding, a continuous peripheral intravenous infusion at a rate of 4-8 mg/kg/min should be given. Bolus injections of hypertonic glucose should be avoided because they may cause further hyperinsulinemia and potentially produce rebound hypoglycemia.

For treatment of hypocalcemia and hypomagnesemia, see Chapter 106; for respiratory distress syndrome treatment, see Chapter 101.3; for treatment of polyhydramnios, see Chapter 103.3.

**PROGNOSIS**

The subsequent incidence of diabetes mellitus in infants of diabetic mothers is higher than that in the general population. Physical development is normal, but oversized infants may be predisposed to childhood obesity that may extend into adult life. Disagreement persists
Screening and Management of Postnatal Glucose Homeostasis in Late Preterm and Term SGA, IDM/LGA Infants

[(LPT) Infants 34–36 wk and SGA (screen 0–24 hrs); IDM and LGA ≥34 weeks (screen 0–12 hrs)]

Asymptomatic

Birth to 4 hours of age
INITIAL FEED WITHIN 1 hour
Screen glucose 30 minutes after 1st feed

Initial screen <25 mg/dL
Feed and check in 1 hour
<25 mg/dL
IV glucose*
25–40 mg/dL
Refeed/IV glucose* as needed

Symptomatic and <40 mg/dL

Birth to 4 hours of age
Continue feeds q2–3 hours
Screen glucose prior to each feed

Screen <35 mg/dL
Feed and check in 1 hour
<35 mg/dL
IV glucose*
35–45 mg/dL
Refeed/IV glucose* as needed

Target glucose screen ≥45 mg/dL prior to feeds
*Glucose dose = 200 mg/kg (dextrose 10% at 2 mL/kg) and/or IV infusion at 5–8 mg/kg per min (80–100 mL/kg per d).
Achieve plasma glucose level of 40–50 mg/dL.

Symptoms of hypoglycemia include: Irritability, tremors, jitteriness, exaggerated Moro reflex, high-pitched cry, seizures, lethargy, floppiness, cyanosis, apnea, poor feeding.

Figure 107-3 Screening for and management of postnatal glucose homeostasis in late-preterm (LPT 34-36 wk) and term small-for-gestational age (SGA) infants and infants who were born to mothers with diabetes (IDM)/large-for-gestational age (LGA) infants. LPT and SGA, screen 0-24 hr; IDM and LGA ≥34 wk, screen 0-12 hr. IV indicates intravenous. (American Academy of Pediatrics Committee of Fetus and Newborn: Postnatal glucose homeostasis in late-preterm and term infants. Pediatrics 127:575-579, 2011, Fig. 1, p. 576.)

about whether these infants have a slightly increased risk of impaired intellectual development unrelated to hypoglycemia; symptomatic hypoglycemia increases the risk, as does maternal ketonuria.

Bibliography is available at Expert Consult.
Bibliography
Chapter 108
Dysmorphology
Anne Slavotinek

Dysmorphology is the study of abnormalities of human form and the mechanisms that cause them. It is estimated that 1 in 40, or 2.5% of newborns, have a recognizable malformation or malformations at birth. In about half of these newborns, a single isolated malformation is found, whereas in the other half, there are multiple malformations. It is estimated that 10% of pediatric hospital admissions involve known genetic conditions, 18% involve congenital defects of unknown etiology, and 40% of surgical admissions are of patients with congenital malformations. Between 20% and 30% of infant deaths and 30-50% of deaths after the neonatal period are a result of congenital abnormalities (http://www.marchofdimes.com/peristats/).

In 2001, birth defects accounted for 1 in 5 infant deaths in the United States, with a rate of 137.6 deaths per 100,000 live births, which is higher than other causes, such as preterm/low birthweight (109.5/100,000), sudden infant death syndrome (55.5/100,000), maternal complications of pregnancy (37.3/100,000), and respiratory distress syndrome (25.3/100,000).

CLASSIFICATION OF BIRTH DEFECTS
Congenital birth defects either are isolated, single defects or manifest as multiple anomalies in a single individual. Single primary defects can be classified according to the nature of the presumed cause of the defect as a malformation, dysplasia, deformation, or disruption (Table 108-1, Fig. 108-1), although most are malformations. Malformations and dysplasias both affect intrinsic structure. A malformation is a primary structural defect arising from a localized error in morphogenesis and resulting in the abnormal formation of a tissue or organ (Fig. 108-1A). Dysplasia refers to an abnormal organization of cells into tissues (Fig. 108-1D). The distinction of a malformation from a dysplasia may be helpful, but there is much overlap. Deformations and disruptions are secondary effects that result from forces generated extrinsic to the affected tissue or organ. A deformation is an alteration in shape or structure of a structure or organ that has differentiated normally (Fig. 108-1B). A disruption is a structural defect resulting from the destruction of a structure that had formed normally before the insult (Fig. 108-1C).

More than 1,000 of the ≈1,750 inherited human disorders with altered morphogenesis display multiple malformations. When several malformations occur in a single individual, they are classified as syndromes, sequences, or associations. A syndrome is defined as a pattern of multiple abnormalities that are related by pathophysiology and result from a single, defined etiology. Sequences consist of multiple malformations that are caused by a single event that can have many etiologies. An association refers to a nonrandom collection of malformations in which there is an unclear or unknown relationship among the malformations such that they do not fit the criteria for a syndrome or sequence.

Malformations and/or Dysplasias
Human malformations and dysplasias are caused by the interactions of genes and environmental factors (Table 108-2; see Fig. 108-1). Some malformations are caused by single-gene defects or abnormalities of multiple genes acting in concert, and the environment causes others. In 1996, it was thought that malformations were caused by monogenic
defects in 7.5% of patients; by chromosomal anomalies in 6%; by multigenic defects in 20%; and by known environmental factors, such as maternal diseases, infections, and teratogens, in 6-7% (Table 108-3); in the remaining 60-70% of patients, malformations were classified as caused by unknown etiologies. A decade later, the percentages were somewhat higher for all categories of known causes of malformations, a change resulting from improved cytogenetic methods for detecting small chromosomal abnormalities as well as techniques for mapping and cloning disease genes. Since the previous edition of this book, it has been discovered that an additional 10-20% of birth defects result from even smaller chromosomal abnormalities detectable by whole genome arrays using comparative genomic hybridization (array CGH) methodology. In spite of these advances, we still do not know the causes for 40-50% of birth defects. Many developmental abnormalities are caused by mutations in a single gene and display characteristic mendelian patterns of inheritance. The molecular etiology for more than 250 single-gene disorders is known. Affected genes are often part of evolutionarily conserved signal transduction pathways, transcription factors, or regulatory proteins required for key developmental events. Some examples are listed in Table 108-2; they include autosomal recessive spondylocostal dysostosis (SCD) syndrome, the autosomal recessive Smith-Lemli-Opitz syndrome (SLOS), the autosomal dominant Rubinstein-Taybi syndrome, and the X-linked lissencephaly (“smooth brain”) syndrome. The SCD syndromes are etiologically heterogeneous and are often caused by mutations in the gene coding for delta-like 3 (DLL3), a ligand of the Notch receptors. The Notch/delta pathway is conserved throughout evolution and regulates a number of developmental events. Patients with SCD display a characteristic pattern of abnormal vertebral segmentation associated with a number of other malformations, such as nerve tube defects. SLOS (Fig. 108-2) results from mutations in the sterol delta-7-dehydrocholesterol reductase (DHCR7) gene, an

**Figure 108-1** The four major types of problems in morphogenesis: malformation, deformation, disruption, and dysplasia. A, An infant with camptometelic dysplasia syndrome, which results in a multiple malformation syndrome caused by a mutation in SOX9. B, An infant with oligohydramnios deformation sequence caused by premature rupture of membranes from 17 wk of gestation until birth at 36 wk; the infant was delivered from persistent transverse lie. C, A fetus with early amnion rupture sequence with attachment of the placenta to the head and resultant disruption of craniofacial structures with distal limb contractures. D, An infant with diastrophic dysplasia caused by inherited autosomal recessive mutations in a sulfate transporter protein. (From Graham Jr JM: Smith’s recognizable patterns of human deformation, ed 3, Philadelphia, 2007, Saunders, Fig. 1-1, p. 4.)

<table>
<thead>
<tr>
<th>TERMINOLOGY</th>
<th>DEFINITION</th>
<th>EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malformation sequence</td>
<td>Single, local tissue morphogenesis abnormality that produces a chain of subsequent defects</td>
<td>DiGeorge sequence of primary fourth branchial arch and 3rd and 4th pharyngeal pouch defects that lead to aplasia or hypoplasia of the thymus and parathyroid glands, aortic arch anomalies, and micrognathia</td>
</tr>
<tr>
<td>Deformation sequence</td>
<td>Mechanical (uterine) forces that alter structure of intrinsically normal tissue</td>
<td>Oligohydramnios produces deformations by in utero compression of limbs (dislocated hips, equinovarus foot deformity), crumpled ears, dislocated nose, or small thorax</td>
</tr>
<tr>
<td>Disruption sequence</td>
<td>In utero tissue destruction after a period of normal morphogenesis</td>
<td>Amnionic membrane rupture sequence, leading to amputation of fingers/toes, tissue fibrosis, and destructive tissue bands</td>
</tr>
<tr>
<td>Dysplasia sequence</td>
<td>Poor organization of cells into tissues or organs</td>
<td>Neurocutaneous melanosis sequence with poor migration of melanocyte precursor cells from the neural crest to the periphery, manifesting as melanocytic hamartosis of skin, meninges, and so forth</td>
</tr>
<tr>
<td>Malformation syndrome</td>
<td>Appearance of multiple malformations in unrelated tissues without an understandable unifying cause; with enhanced genetic investigation, a single etiology may become identified</td>
<td>Trisomy 21 Teratogens</td>
</tr>
</tbody>
</table>

Examples of Malformations with Distinct Causes, Clinical Features, and Pathogenesis

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>CAUSE/INHERITANCE</th>
<th>CLINICAL FEATURES</th>
<th>PATHOGENESIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spondylocostal dysostosis syndromes</td>
<td>Mendelian autosomal recessive</td>
<td>Abnormal vertebral segmentation, Neural tube defects</td>
<td>DLL3 mutations; mutations can also be present in other genes</td>
</tr>
<tr>
<td>Rubinstein-Taybi syndrome</td>
<td>Mendelian autosomal recessive</td>
<td>Mental retardation, Broad thumbs, toes, Hypoplastic maxillae, Prominent nose, Congenital heart disease</td>
<td>CBP mutations or haploinsufficiency</td>
</tr>
<tr>
<td>X-linked lissencephaly</td>
<td>Mendelian X-linked</td>
<td>Male: Severe mental retardation, Seizures, Female: Variable</td>
<td>DCX mutation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Cause/Inheritance</th>
<th>Clinical Features</th>
<th>Pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aniridia</td>
<td>Autosomal semidominant</td>
<td>Reduced or absent iris</td>
<td>PAX6 mutations</td>
</tr>
<tr>
<td>Waardenburg syndrome</td>
<td>Autosomal semidominant</td>
<td>Deafness, White forelock, Wide-spaced eyes, Pale eye pigment</td>
<td>PAX3 mutations, MITF mutations</td>
</tr>
<tr>
<td>Holoprosencephaly</td>
<td>Loss of function or heterozygosity</td>
<td>Microcephaly, Cyclopia, Single central incisor</td>
<td>SHH mutations</td>
</tr>
<tr>
<td>Velo-cardio-facial syndrome</td>
<td>Microdeletion 22q11.2</td>
<td>Conotruncal congenital heart disease, Cleft palate, T-cell defects, Facial anomalies</td>
<td>TBX1 haploinsufficiency/mutations; haploinsufficiency for other genes in the deleted interval</td>
</tr>
<tr>
<td>Down syndrome</td>
<td>Chromosomal</td>
<td>Mental retardation, Characteristic dysmorphic features, Congenital heart disease, Increased risk of leukemia, Alzheimer disease</td>
<td>50% increase of estimated 250 genes on chromosome 21</td>
</tr>
<tr>
<td>Neural tube defects</td>
<td>Multifactorial</td>
<td>Meningomyelocele</td>
<td>Defects in folate sensitive enzymes or folic acid uptake</td>
</tr>
<tr>
<td>Fetal alcohol syndrome</td>
<td>Teratogenic</td>
<td>Microcephaly, Developmental delay, Facial abnormalities, Behavioral abnormalities</td>
<td>Ethanol toxicity to developing brain</td>
</tr>
<tr>
<td>Retinoic acid embryopathy</td>
<td>Teratogenic</td>
<td>Microtia, Congenital heart disease</td>
<td>Isotretinoin effects on neural crest and branchial arch development</td>
</tr>
</tbody>
</table>

enzyme important in cholesterol biosynthesis. Patients with SLOS display syndactyly (fusion of the fingers and toes), polydactyly, an upturned (anteverted) nose, ptosis, cryptorchidism, and holoprosencephaly. These mutations link cholesterol biosynthesis pathogenetically to the sonic hedgehog (SHH) pathway, because many of the features of the former disorder are related to defects in SHH, which is posttranslationally modified by cholesterol (see Chapter 86). Rubinstein-Taybi syndrome (see Fig. 108-2) results from heterozygous, loss-of-function mutations in the gene coding for a broadly acting transcriptional coactivator called CBP, or CREB-binding protein. The CBP coactivator regulates the transcription of a number of genes, a fact that helps explain why patients with mutations in CBP have a wide-ranging phenotype that includes mental retardation, broad thumbs and toes, and congenital heart disease. One of the transcription factors that binds to CBP is GLI3, a transcription factor that is part of the SHH pathway (see Fig. 108-2). X-linked lissencephaly—a severe neuronal migration defect that in males causes a smooth brain with reduction or absence of gyri and sulci and in females gives rise to a variable pattern of mental retardation and seizures—is caused by mutations in DCX. The DCX protein regulates the activity of dynein motors and moves the nucleus during neuronal migration.

Other malformation syndromes are caused by chromosomal imbalance, multifactorial inheritance, and teratogens (see Tables 108-2 and 108-3). Down syndrome results from an extra dose of part or all of chromosome 21, a small chromosome that contains ≈200 known or predicted genes. It is most commonly caused by trisomy 21, which means that individuals with Down syndrome have an increased dose of as many as 250 genes contained on this chromosome (see Chapter 81.1). Neural tube defects (NTDs) are an example of a disorder that displays multifactorial inheritance in the majority of cases. NTDs and can result from a combination of dietary deficiencies and increased utilization during pregnancy as well as from a common variant in the gene for an enzyme in the folate recycling pathway,
Table 108-3 Causes of Congenital Malformations

<table>
<thead>
<tr>
<th>MONOGENIC (7.5% of major anomalies)</th>
<th>X-linked hydrocephalus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Achondroplasia</td>
</tr>
<tr>
<td></td>
<td>Ectodermal dysplasia</td>
</tr>
<tr>
<td></td>
<td>Apert syndrome</td>
</tr>
<tr>
<td></td>
<td>Treacher Collins syndrome</td>
</tr>
<tr>
<td>CHROMOSOMAL (6% of major anomalies)</td>
<td>Trisomy 21, 18, 13</td>
</tr>
<tr>
<td></td>
<td>XO, XXY</td>
</tr>
<tr>
<td></td>
<td>Deletions 4p−, 5p−, 7q−, 13q−, 18p−, 18q−, 22q−</td>
</tr>
<tr>
<td></td>
<td>Prader-Willi syndrome (50% of affected patients have deletion of chromosome 15)</td>
</tr>
<tr>
<td>MATERNAL INFECTION (2% of major anomalies)</td>
<td>Intrauterine infections (e.g., herpes simplex virus, cytomegalovirus, varicella-zoster virus, rubella virus, and toxoplasmosis)</td>
</tr>
<tr>
<td>MATERNAL ILLNESS (3.5% of major anomalies)</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Phenylketonuria</td>
</tr>
<tr>
<td></td>
<td>Hyperthermia</td>
</tr>
<tr>
<td>UTERINE ENVIRONMENT (% unknown)</td>
<td>Deformation</td>
</tr>
<tr>
<td></td>
<td>Uterine pressure, oligohydramnios: clubfoot, torticollis, congenital hip dislocation, pulmonary hypoplasia, 7th nerve palsy</td>
</tr>
<tr>
<td></td>
<td>Disruption</td>
</tr>
<tr>
<td></td>
<td>Amniotic bands, congenital amputations, gastrochisis, porencephaly, intestinal atresia</td>
</tr>
<tr>
<td></td>
<td>Twinning</td>
</tr>
<tr>
<td>ENVIRONMENTAL AGENTS (% unknown)</td>
<td>Polychlorinated biphenyls</td>
</tr>
<tr>
<td></td>
<td>Herbicides</td>
</tr>
<tr>
<td></td>
<td>Mercury</td>
</tr>
<tr>
<td></td>
<td>Alcohol</td>
</tr>
<tr>
<td>MEDICATIONS (% unknown)</td>
<td>Thalidomide</td>
</tr>
<tr>
<td></td>
<td>Diethylstilbestrol</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
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<tr>
<td></td>
<td>Warfarin</td>
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<tr>
<td></td>
<td>Cytotoxic drugs</td>
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<tr>
<td></td>
<td>Paroxetine</td>
</tr>
<tr>
<td></td>
<td>Angiotensin-converting enzyme inhibitors</td>
</tr>
<tr>
<td></td>
<td>Isotretinoin (vitamin A)</td>
</tr>
<tr>
<td></td>
<td>D-Penicillamine</td>
</tr>
<tr>
<td></td>
<td>Valproic acid</td>
</tr>
<tr>
<td>UNKNOWN ETIOLOGIES</td>
<td>Polygenetic</td>
</tr>
<tr>
<td></td>
<td>Associated with infertility (spontaneous or with treatment)</td>
</tr>
<tr>
<td></td>
<td>Anencephaly/spina bifida</td>
</tr>
<tr>
<td></td>
<td>Cleft lip/palate</td>
</tr>
<tr>
<td></td>
<td>Pyloric stenosis</td>
</tr>
<tr>
<td></td>
<td>Congenital heart disease</td>
</tr>
<tr>
<td>SPORADIC SYNDROME COMPLEXES</td>
<td>VATER (vertebral defects, anal atresia, tracheoesophageal fistula with esophageal atresia, and radial and renal anomalies) syndrome</td>
</tr>
<tr>
<td></td>
<td>Pierre Robin syndrome</td>
</tr>
<tr>
<td></td>
<td>Prune-belly syndrome</td>
</tr>
<tr>
<td>NUTRITIONAL</td>
<td>Low folic acid–neural tube defects</td>
</tr>
</tbody>
</table>


5,10-methylene-tetrahydrofolate reductase, that makes this enzyme less stable. These discoveries led to the recommendation that all women supplement their diets with 400-800 μg of folic acid per day 1 mo before pregnancy and during the 1st 2 mo of pregnancy. This supplementation has resulted in a reduction in the incidence of NTDs by 75%. Several teratogenic causes of birth defects have been described (see Tables 108-2 and 108-3). Ethanol causes a recognizable malformation syndrome called fetal alcohol syndrome (see Chapter 106.2). Children with fetal alcohol syndrome display microcephaly, developmental delay, hyperactivity, and facial dysmorphic features. Ethanol, which is toxic to the developing central nervous system, causes cell death in developing neurons.

Deformations

Most deformations involve the musculoskeletal system (see Figs. 108-1B and 108-3). Fetal movement is required for the proper development of the normal musculoskeletal system, and anything that restricts fetal movement can cause a musculoskeletal deformation from intrauterine molding. It is important to recognize that deformations can be caused by problems either intrinsic or extrinsic to the developing fetus. Two major intrinsic causes of deformations are primary neuromuscular disorders and oligohydramnios, or decreased amniotic fluid, which is caused by renal defects. The major extrinsic causes of deformation are those that result in fetal crowding to restrict fetal movement. Examples of such extrinsic causes are oligohydramnios from chronic leakage of amniotic fluid, breech presentation (see Figs. 108-1A and 108-4), and abnormal shape of the amniotic cavity. When a fetus is in the breech position, the incidence of deformations is increased 10-fold. The shape of the amniotic cavity has a profound effect on the shape of the fetus and is influenced by many factors, including uterine shape; volume of amniotic fluid; size and shape of the fetus; presence of more than 1 fetus; site of placentation; presence of uterine tumors; shape of the abdominal cavity, which is influenced by the pelvis, sacral promontory, and neighboring abdominal organs; and tightness of the abdominal musculature.

It is important to determine whether deformations result from intrinsic or extrinsic causes. Most children with deformations from extrinsic causes are otherwise completely normal, and their prognosis is usually excellent. Correction usually occurs spontaneously. Deformations caused by intrinsic factors, such as multiple joint contractures resulting from central nervous system defects, would have a different prognosis and a far greater significance for the child.

Disruption

Disruption defects are caused by destruction of a previously normally formed part. At least 2 basic mechanisms are known to produce disruption. One involves entanglement followed by tearing apart or amputation of a normally developed structure, usually a digit, arm, or leg, by strands of amnion floating within amniotic fluid (amniotic bands) (see Figs. 108-1C and 108-5). The second involves interruption of the blood supply to a developing part, which can lead to infarction, necrosis, and/or resorption of structures distal to the insult. If interruption of the blood supply occurs early in gestation, the disruptive defect seen at term usually involves atresia, or absence of a particular part. If the infarction occurs later, necrosis is more likely to be present. Genetic factors usually play a minor role in the pathogenesis of disruptions; most are sporadic events in otherwise normal families. The prognosis for a disruptive defect is determined entirely by the extent and location of the tissue loss.

Multiple Anomalies: Syndrome and Sequence

The pattern of multiple anomalies that occurs when a single primary defect in early morphogenesis produces multiple abnormalities through a cascading process of secondary and tertiary errors in morphogenesis is called a sequence (see Figs. 108-6 and 108-7). When evaluating a child with multiple anomalies, the physician must differentiate multiple anomalies secondary to a single localized error in morphogenesis (a sequence) from a multiple malformation syndrome. In the former, recurrence risk counseling for the multiple anomalies depends entirely on the risk of recurrence for the single localized malformation. The Pierre-Robin malformation sequence is a pattern of multiple anomalies produced by mandibular hypoplasia. Because the tongue is relatively large for the oral cavity, it drops back (glossoptosis), blocks closure of the posterior palatal shelves, and causes a
U-shaped cleft palate. There are numerous causes of mandibular hypoplasia, all of which can result in characteristic features of Pierre-Robin sequence.

**MOLECULAR MECHANISMS OF MALFORMATIONS**

**Inborn Errors of Development**

The genes mutated in malformation syndromes (as well as genes whose expression is disrupted by environmental agents or teratogens) are part of evolutionarily conserved signal transduction pathways, transcription factors, or regulatory proteins required for key developmental events. We should consider malformations to be inborn errors of development. Consideration of malformations as alterations of important developmental pathways provides a molecular framework for understanding human birth defects.

**Sonic Hedgehog Pathway as Model**

The SHH pathway is developmentally important during embryogenesis to induce controlled proliferation in a tissue-specific manner; disruption of specific steps in this pathway results in a variety of related developmental disorders and malformations (see Fig. 108-2). Activation of this pathway in the adult leads to abnormal proliferation and cancer. The SHH pathway transduces an external signal in the form of a ligand into changes in gene transcription by binding of the ligand to specific cellular receptors. SHH is a ligand expressed in the embryo in a variety of areas important for development of the brain, face, limbs, and the gut. Sporadic and inherited mutations are found to cause holoprosencephaly (see Figs. 108-2 and 108-6), a variably severe midline defect with phenotypes ranging from a single maxillary incisor with hypotelorism to cyclopia. SHH is processed by proteolytic cleavage to an active N-terminal form, which is then further modified by the addition of cholesterol. Defects in cholesterol biosynthesis, in particular the sterol delta-7-dehydrocholesterol reductase gene, result in SLOS (see Fig. 108-2). SLOS is also associated with holoprosencephaly.

The modified and active form of SHH binds to its transmembrane receptor Patched (PTCH); there are 2 family members: PTCH1 and PTCH2. SHH binding to PTCH inhibits the activity of the transmembrane protein Smoothened (SMOH). SMOH act to suppress downstream targets of the SHH pathway, the GLI family of transcription factors, so inhibition of SMOH by PTCH results in activation of GLI1, GLI2, and GLI3, resulting in alteration of transcription of GLI targets. Somatic inactivating mutations in PTCH1 and PTCH2 act as tumor suppressors, whereas activating mutations in SMOH function as oncogenes, particularly in basal cell carcinomas and medulloblastomas. Germline inactivating mutations in PTCH1 result in **Gorlin syndrome** (see Fig. 108-2), an autosomal dominant disorder characterized by dysmorphic features (short metacarpals, rib defects, broad face, and dental abnormalities), basal cell nevi that undergo malignant transformation, and an increased risk of cancers such as rhabdomyosarcoma and medulloblastoma. GLI1 amplification has been found in several human tumors, including glioblastoma, osteosarcoma, rhabdomyosarcoma, and B-cell lymphomas; mutations or alterations in GLI3 have been found in Greig cephalopolysyndactyly syndrome (GCPS), **Pallister-Hall syndrome** (PHS), and postaxial polydactyly type A (and

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**Figure 108-2** Mutations in genes that function together in a genetic developmental pathway commonly have overlapping clinical manifestations. Several components of the sonic hedgehog (SHH) pathway have been identified, and their relationships elucidated (see text for further details). Mutations in several members of this pathway result in phenotypes that have facial dysmorphisms, seen in holoprosencephaly, SLOS, Gorlin syndrome, Greig cephalopolysyndactyly syndrome, Pallister-Hall syndrome, and Rubinstein-Taybi syndrome.
A/B) and preaxial polydactyly type IV (see Fig. 108-2). GCPS consists of hypertelorism, syndactyly, preaxial polydactyly, and broad thumbs and great toes. PHS is an autosomal dominant disorder characterized by postaxial polydactyly, syndactyly, hypothalamic hamartomas, imperforate anus, and, occasionally, holoprosencephaly. GLI3 binds to CBP, the protein that is haploinsufficient in the Rubinstein-Taybi syndrome. Disorders that are caused by mutations in genes that function together in a genetic developmental pathway commonly have overlapping clinical manifestations. These overlapping manifestations result from the expression domains of SHH important for development of the brain, face, limbs, and gut in the embryo. Brain defects are found in holoprosencephaly, SLOS, and PHS. Facial abnormalities are found in holoprosencephaly, Gorlin syndrome, GCPS, and PHS. Limb defects are found in SLOS, Gorlin syndrome, GCPS, PHS, and the polydactyly syndromes. Overexpression or activating mutations of the SHH pathway results in cancer, including basal cell carcinoma, medulloblastoma, glioblastoma, and rhabdomyosarcoma.

![Image](image-url)

**Figure 108-3** Deformation abnormalities resulting from uterine compression. *(From Kliegman RM, Jenson HB, Marcdante KJ, et al, editors: Nelson essentials of pediatrics, ed 5, Philadelphia, 2005, Saunders.)*

![Image](image-url)

**Figure 108-4** Breech deformation sequence.

![Image](image-url)

**Figure 108-5** A, Amniotic band disruption sequence. B, Bands constricting the ankle leading to deformational defects and amputations. *(From Jones KJ: Smith’s recognizable patterns of human malformation, ed 6, Philadelphia, 2006, Saunders.)*
The SHH pathway has been shown to interact with the primary cilium, and this interaction is critical to transduce the SHH extracellular signal through to the nuclear machinery. In fact, a host of disorders, including Bardet-Biedl syndrome, oral facial digital syndrome type 1, and Joubert syndrome, are known to be caused by mutations in genes that function in the primary cilium (Table 108-4). These disorders overlap phenotypically with a number of the phenotypes described previously, again demonstrating that perturbations of conserved developmental pathways cause overlapping phenotypes.

**Chromosomal Imbalances**

It has been recognized for more than 50 yr that genomic imbalances that result from an additional copy of 1 whole human chromosome can result in a characteristic and recognizable syndrome. As previously discussed, an additional copy of chromosome 21 results in Down syndrome (see Chapter 81); loss of 1 of the X chromosomes results in Turner syndrome (see Chapter 81 for discussion of syndromes with whole chromosomal imbalances). With the advent of higher-resolution cytogenetics techniques and standardization of chromosome identification using chromosomal preparations, it became possible to identify subchromosomal deletions and duplications. A number of recurrent deletions and duplications were identified that resulted in characteristic and recognizable syndrome (see Chapter 81, Table 81-12), such as Williams syndrome (deletion of 7q11.23), Miller-Dieker syndrome (deletion of 17p13.3), Smith-Magenis syndrome (deletion of 17p11.2), and velocardiofacial/DiGeorge syndrome (deletion of 22q11.2). Array CGH (or single-nucleotide polymorphism–based genotyping with dosage detection) has made it possible to uncover smaller microdeletions and microduplications associated with various birth defects, mental retardation, and neuropsychiatric disorders. The sensitivity and
specifi city of array CGH has made it the technique of choice for the initial evaluation of a child with multiple congenital anomalies and/or mental retardation, although it is important to note that all individuals carry dozens of small microdeletions and microduplications as normal variants. Therefore, it is important to examine any of these findings in children with birth defects with parents and with databases of normal variants detected in individuals without such birth defects. Array CGH is the preferred method for detecting possible genomic abnormalities associated with multiple congenital anomalies and/or mental retardation.

**APPRAOCH TO THE DYSMORPHIC CHILD**

One approach to the dysmorphic child is the pattern-recognition approach, which compares the manifestations in the patient against an enormous and memorized (or computerized) knowledge of human pleiotropic disorders. Although this approach can be appropriate for a small number of experienced dysmorphologists, the systematic genetic-mechanism approach can be used by clinicians who are not experts in dysmorphology. By gathering and analyzing these clinical data, the general pediatrician can either diagnose the patient in the straightforward case or initiate a referral process to an appropriate expert.

**History**

The history for a child with birth defects includes a number of elements that are related to etiologic factors. The first is the pedigree or family history that is necessary to assess the inheritance pattern, or lack thereof, of the disorder. For disorders that have simple mendelian inheritance patterns, the recognition of that pattern can be critical to help narrow the differential diagnosis. A number of common birth defects have complex genetic contributions, such as isolated cleft palate and spina bifida. The recognition of a close relative (or the fetus of a close relative) affected with a birth defect that is similar to that of the proband can be quite useful. A 3-generation pedigree is sufficient for this purpose (see Chapter 80).

The perinatal history is an essential component of the history (see Chapter 94.1). It includes the pregnancy history of the mother (useful for recognition of recurrent miscarriages that may be a sign of a familial chromosomal disorder), factors that may relate to deformations or disruptions (oligohydramnios), and maternal exposures to teratogenic drugs or chemicals (methyl mercury, isotretinoin, and ethanol are potential causes of microcephaly). Although recognition of known teratogens is an important part of the history, it is important to know that many more agents are impugned as teratogenic than are confirmed as such. Physicians are encouraged to consult experts in teratology and expert information sources such as Teris (http://depts.washington.edu/~terisweb/teris) to analyze specific potential teratogens.

One final component to the history that is often useful is the natural history of the phenotype. Malformation syndromes caused by chromosomal aneuploidy or aneuploidy and single-gene pleiotropic disorders are usually static. Although the patients can experience new complications in time, the phenotype is not progressive. In contrast, disorders that cause dysmorphic features by the mechanism of metabolic perturbations (e.g., Hunter syndrome, Sanfilippo syndrome) are either mild or not apparent at birth and progress relentlessly, causing deterioration of the patient over time.

**Physical Examination**

The physical examination is essential to the diagnosis of a dysmorphic syndrome. The essential element of the evaluation is objective assessment of the structure of the child. The clinician needs to perform an organized and systematic cataloguing of the size and structure of various body structures. Familiarity with the nomenclature of dysmorphic signs is helpful (Table 108-5). The size and shape of the head is relevant, as many children with Down syndrome have mild microcephaly and brachycephaly (shortened anteroposterior dimension of the skull). Eye position and shape are useful signs for many disorders. There are a number of reference standards with which pediatric physical measurements (e.g., interpupillary distance) can be compared. It is also useful to categorize abnormalities as “major” or “minor” birth defects. The former are those that either cause dysfunction (absence of a digit) or require surgical correction (polydactyly), and the latter those that cause neither significant dysfunction nor require surgical correction (mild cutaneous syndactyly) (Table 108-6 and Fig. 108-8). By cataloging every available physical parameter, the clinician can recognize the diagnosis or at least have enough information for intelligent discussion of the patient with a consultant.

**Imaging Studies**

Imaging studies can be critical in the diagnosis of a dysmorphic disorder. If short stature or disproportionate stature (long trunk and short limbs) is noted, a full skeletal survey should be performed. The skeletal survey can yield numerous abnormal features that can be used to narrow the differential diagnosis. When there are abnormal neurologic signs or symptoms, central nervous system imaging is indicated. Some
Table 108-4  Childhood Diseases and Syndromes Associated with Motile and Sensory Ciliopathies

<table>
<thead>
<tr>
<th>PEDiATRIC CIlioPATHY</th>
<th>CLINICAL MANIFESTATIONS</th>
<th>GENE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MOTOR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary ciliary dyskinesia</td>
<td>Chronic bronchitis, rhinosinusitis, otitis media, laterality</td>
<td>DNA11, DNAH5, DNAH11, DNAI2, KTU, TXNDC3,</td>
</tr>
<tr>
<td></td>
<td>defects, infertility, CHD</td>
<td>LRRCS0, RSPH9, RSPH4A, CCDC40, CCDC39</td>
</tr>
<tr>
<td><strong>SENSORY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autosomal recessive polycystic</td>
<td>RFD, CHF</td>
<td>PKHD1</td>
</tr>
<tr>
<td>kidney disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephronophthisis</td>
<td>RFD, interstitial nephritis, CHF, RP</td>
<td>NPHP1-8, ALMS1, CEP290</td>
</tr>
<tr>
<td>Bardet-Biedl syndrome</td>
<td>Obesity, polydactyly, ID, RP, renal anomalies, anosmia, CHD</td>
<td>BBS1-12, MKS1, MKS3, CEP290</td>
</tr>
<tr>
<td>Meckel-Gruber syndrome</td>
<td>RFD, polydactyly, ID, CNS anomalies, CHD, cleft lip, cleft</td>
<td>MKS1-6, CC2D2A, CEP290, TMEM216</td>
</tr>
<tr>
<td></td>
<td>palate</td>
<td></td>
</tr>
<tr>
<td>Joubert syndrome</td>
<td>CNS anomalies, ID, ataxia, RP, polydactyly, cleft lip, cleft</td>
<td>NPHP1, JBTS1, JBTS3, JBTS4, COR2S, AH1, CEP290, TMEM216</td>
</tr>
<tr>
<td>Alstrom syndrome</td>
<td>Obesity, RP, DM, hypothyroidism, hypogonadism, skeletal</td>
<td>ALMS1</td>
</tr>
<tr>
<td></td>
<td>dysplasia, cardiomyopathy, pulmonary fibrosis</td>
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<td>Orofaciocutaneous syndrome type</td>
<td>Polydactyly, syndactyly, cleft lip, cleft palate, CNS</td>
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</tr>
<tr>
<td>1</td>
<td>anomalies, ID, RFD, CHF</td>
<td></td>
</tr>
<tr>
<td>Ellis van Creveld syndrome</td>
<td>Chondrodysplasty, polydactyly, ectodermal dysplasia, CHD</td>
<td>EVC, EVC2</td>
</tr>
<tr>
<td>Jeune asphyxiating thoracic</td>
<td>Narrow thorax, RFD, dwarfism, polydactyly</td>
<td>IFT80</td>
</tr>
<tr>
<td>dystrophy</td>
<td></td>
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</tr>
<tr>
<td>Sensenbrenner syndrome</td>
<td>Dolichocephaly, ectodermal dysplasia, dental dysplasia,</td>
<td>IFT122, IFT43, WDR35</td>
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<tr>
<td></td>
<td>narrow thorax, RFD, CHD</td>
<td></td>
</tr>
<tr>
<td>Short rib-polydactyly syndromes</td>
<td>Narrow thorax, short limb dwarfism, polydactyly, renal</td>
<td>WDR35, DYNC2H1, NEK1</td>
</tr>
<tr>
<td></td>
<td>dysplasia</td>
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</tr>
</tbody>
</table>

CHD, congenital heart disease; CHF, congenital hepatic fibrosis; CNS, central nervous system; DM, diabetes mellitus; ID, intellectual disabilities; RFD, renal fibrocystic disease; RP, retinitis pigmentosa.


Table 108-5  Definitions of Common Clinical Signs of Dysmorphic Syndromes

<table>
<thead>
<tr>
<th>SIGN</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachycephaly</td>
<td>A condition in which head shape is shortened from front to back along the sagittal plane; the back of the skull and face are flatter than normal</td>
</tr>
<tr>
<td>Brachydactyly</td>
<td>A condition of having short digits</td>
</tr>
<tr>
<td>Brushfield spots</td>
<td>Speckled white rings about ½ of the distance to the periphery of the iris of the eye</td>
</tr>
<tr>
<td>Camptodactyly</td>
<td>Permanent flexion of one or more fingers associated with missing inner phalangeal creases indicating lack of finger movement from before 8 wk of gestation</td>
</tr>
<tr>
<td>Clinodactyly</td>
<td>A medial or lateral curving of the fingers; usually refers to incurring of the 5th finger</td>
</tr>
<tr>
<td>Hypoplastic nail</td>
<td>An unusually small nail on a digit</td>
</tr>
<tr>
<td>Low-set ears</td>
<td>This designation is made when the helix meets the cranium at a level below a horizontal plane that is an extension of a line through both inner canthi</td>
</tr>
<tr>
<td>Melia</td>
<td>A suffix meaning “limb” (e.g., amelia—missing limb; brachymelia—short limb)</td>
</tr>
<tr>
<td>Ocular hypertelorism</td>
<td>Increased distance between the pupils of the 2 eyes, also known as increased interpupillary distance</td>
</tr>
<tr>
<td>Plagiocephaly</td>
<td>A condition in which head shape is asymmetric in the sagittal or coronal plane that can result from asymmetry in suture closure or from asymmetry of brain growth</td>
</tr>
<tr>
<td>Posterior parietal hair whorl</td>
<td>A single whorl occurs to the right or left of midline and within 2 cm anterior to the posterior fontanel in 95% of cases. The whorl represents the focal point from which the posterior scalp skin was under growth tension during brain growth between the 10th and 16th wk of fetal development. Aberrant position of the whorl reflects an early defect in brain development</td>
</tr>
<tr>
<td>Postaxial polydactyly</td>
<td>Extra finger or toe present on the lateral side of the hand or foot</td>
</tr>
<tr>
<td>Preaxial polydactyly</td>
<td>Extra finger or toe present on the medial side of the hand or foot</td>
</tr>
<tr>
<td>Prominent lateral palatine ridges</td>
<td>Relative overgrowth of the lateral palatine ridges secondary to a deficit of tongue thrust into the hard palate</td>
</tr>
<tr>
<td>Scaphocephaly</td>
<td>A condition in which the head is elongated from front to back in the sagittal plane; most normal skulls are scaphocephalic. Also termed dolichocephaly.</td>
</tr>
<tr>
<td>Shawl scrotum</td>
<td>The scrotal skin joins around the superior aspect of the penis and represents a mild deficit in full migration of the labial-scrotal folds</td>
</tr>
<tr>
<td>Short palpebral fissures</td>
<td>Decreased horizontal distance of the eyelid folds based on measurement from the inner to the outer canthus</td>
</tr>
<tr>
<td>Syndactyly</td>
<td>Incomplete separation of the fingers. It most commonly occurs between the 3rd and 4th fingers and between the 2nd and 3rd toes</td>
</tr>
<tr>
<td>Synophrys</td>
<td>Eyebrows that meet in the midline</td>
</tr>
<tr>
<td>Telecanthus</td>
<td>Lateral displacement of the inner canthi. The inner canthal distance (ICD) is increased, but the interpupillary distance (IPD) is normal.</td>
</tr>
<tr>
<td>Widow's peak</td>
<td>V-shaped midline, downward projection of the scalp hair in the frontal region. It represents an upper forehead intersection of the bilateral fields of periorbital hair growth suppression. It usually occurs because the fields are widely spaced, as in ocular hypertelorism</td>
</tr>
</tbody>
</table>
Part XII  Minor Anomalies and Phenotype Variants*

Clinical Indications for Chromosome diagnosis and therapy, major anomaly is 20-30\%.

If 3 minor anomalies are present, the probability that there is a underlying syndrome or a major anomaly (congenital heart anomalies, and 0.5\% have 3 minor anomalies. If 2 minor anomalies are present, *Approximately 15\% of newborns have 1 minor anomaly, 0.8\% have 2 minor anomalies, and 0.5\% have 3 minor anomalies. If 2 minor anomalies are present, the probability of an underlying syndrome or a major anomaly (congenital heart disease, renal, central nervous system, limbic) is 5-fold that in the general population. If 3 minor anomalies are present, the probability that there is a major anomaly is 20-30%.


### Table 108-6 Minor Anomalies and Phenotype Variants*

<table>
<thead>
<tr>
<th>CRANIOFACIAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large fontanel</td>
</tr>
<tr>
<td>Flat or low nasal bridge</td>
</tr>
<tr>
<td>Saddle nose, upturned nose</td>
</tr>
<tr>
<td>Mild micrognathia</td>
</tr>
<tr>
<td>Cutis aplasia of scalp</td>
</tr>
<tr>
<td>EYE</td>
</tr>
<tr>
<td>Inner epicanthal folds</td>
</tr>
<tr>
<td>Telecanthus</td>
</tr>
<tr>
<td>Slanting of palpebral fissures</td>
</tr>
<tr>
<td>Hypertelorism</td>
</tr>
<tr>
<td>Brushfield spots</td>
</tr>
<tr>
<td>SKIN</td>
</tr>
<tr>
<td>Dimpling over bones</td>
</tr>
<tr>
<td>Capillary hemangioma (face, posterior neck)</td>
</tr>
<tr>
<td>Dermal melanosis (African Americans, Asians)</td>
</tr>
<tr>
<td>Sacral dimple</td>
</tr>
<tr>
<td>Pigmented nevi</td>
</tr>
<tr>
<td>Redundant skin</td>
</tr>
<tr>
<td>Cutis marmorata</td>
</tr>
<tr>
<td>HAND</td>
</tr>
<tr>
<td>Simian creases</td>
</tr>
<tr>
<td>Bridged upper palmar creases</td>
</tr>
<tr>
<td>Clinodactyly of 5th digit</td>
</tr>
<tr>
<td>Hypertensibility of thumbs</td>
</tr>
<tr>
<td>Single flexion crease of 5th digit (hypoplasia of middle phalanx)</td>
</tr>
<tr>
<td>Partial cutaneous syndactyly</td>
</tr>
<tr>
<td>Polydactyly</td>
</tr>
<tr>
<td>Short, broad thumb</td>
</tr>
<tr>
<td>Narrow, hyperconvex nails</td>
</tr>
<tr>
<td>Hypoplastic nails</td>
</tr>
<tr>
<td>Camptodactyly</td>
</tr>
<tr>
<td>Shortened 4th digit</td>
</tr>
<tr>
<td>FOOT</td>
</tr>
<tr>
<td>Partial syndactyly of 2nd and 3rd toes</td>
</tr>
<tr>
<td>Asymmetric toe length</td>
</tr>
<tr>
<td>Clinodactyly of 2nd toe</td>
</tr>
<tr>
<td>Overlapping toes</td>
</tr>
<tr>
<td>Nail hypoplasia</td>
</tr>
<tr>
<td>Wide gap between hallux and 2nd toe (wide sandal gap)</td>
</tr>
<tr>
<td>Deep plantar crease between hallux and 2nd toe</td>
</tr>
<tr>
<td>OTHERS</td>
</tr>
<tr>
<td>Mild calcaneovalgus</td>
</tr>
<tr>
<td>Hydrocele</td>
</tr>
<tr>
<td>Shawl scrotum</td>
</tr>
<tr>
<td>Hypoplasia of labia major</td>
</tr>
</tbody>
</table>

Table 108-7 Clinical Indications for Chromosome Analysis, or Array CGH*

<table>
<thead>
<tr>
<th>Number of minor malformations per newborn</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3 or more</td>
</tr>
</tbody>
</table>

*Note: These are guidelines, and prudence dictates the use of the chromosome analysis in cases that may not meet these general guidelines. The guidelines are for situations in which such an analysis is strongly recommended.

children with microcephaly will be recognized to have abnormal cortical migration (lissencephaly), a discovery that markedly narrows the differential diagnosis for microcephaly. Other studies, such as echocardiography and renal ultrasonography, can be useful to identify additional major or minor malformations.

### Laboratory Studies

The laboratory evaluation of the dysmorphic child is helpful but complex. Cytogenetics with a Giemsa-banded (G-banded) peripheral leukocyte karyotype (or chromosome) analysis was the gold standard and was previously performed in most evaluations of the dysmorphic child (Table 108-7). Array CGH and single-nucleotide polymorphism genotyping with copy number variation (dosage detection) are the most sensitive methods for the detection of cytogenomic alterations associated with multiple congenital anomalies. A practical reason for ordering cytogenetic studies early in the diagnostic process is that it typically takes 7-12 days for results.

Molecular testing for mutations that cause pleiotropic developmental anomaly syndromes is available for many disorders. In most cases, however, such testing should not be performed as a screening test, but instead should be ordered thoughtfully after the differential diagnosis has been narrowed. High-throughput genomic DNA sequencing (exome sequencing or whole genome sequencing) are increasingly used as a diagnostic tool.

Historically, dysmorphic and metabolic disorders were considered distinct classes of disease. However, as in the case of the SLOS, metabolic abnormalities of the fetus can cause malformations. A general metabolic screen should be performed unless the differential diagnosis leads the clinician to strongly suspect a non-metabolic disease.

### Diagnosis

The examining physician should gather data on the patient’s pedigree and perinatal and pediatric (for older children) history and should
have an appreciation for the natural history of the disorder. At this point, the physician has examined the child, identified abnormal physical features, and obtained appropriate imaging studies and preliminary interpretations.

The clinician should now organize the findings by their specificity into potential developmental pathophysiologic processes. The specificity assessment is the simplest. If a child has a patent ductus arteriosus, mild growth retardation, mild microcephaly, and holoprosencephaly (MRI finding of failure to lateralize the forebrain), microopenis, and ptosis, these findings can be prioritized. The patent ductus arteriosus, ptosis, mild growth retardation, and mild microcephaly are nonspecific findings (present in many disorders or often present as isolated features not part of a syndrome), whereas holoprosencephaly and microopenis are present in fewer syndromes and are never normal variants. With this recognition, the clinician can search for disorders that include both holoprosencephaly and microopenis. The search can be performed manually using the features index of a textbook such as Smith's Recognizable Patterns of Human Malformation or a computerized database such as the Winter-Baraitser Dysmorphology Database (www.lmdatabases.com/about_lmd.html). Searching for disorders with both findings leads quickly to a modest list of only 21 disorders. One of these is SLOS. The identification of this possible diagnosis prompts the physician to return to the bedside, realize that many of the nonspecific features in the child are common in SLOS, and make a tentative diagnosis of this disorder. Although holoprosencephaly is an uncommon manifestation of SLOS, this manifestation makes sense because of the known pathogenetic link between sonic hedgehog and cholesterol biosynthesis. Because this disorder is caused by mutations in the sterol delta-7-dehydrocholesterol reductase gene and is associated with elevated 7-dehydrocholesterol, the pediatrician can initiate a consultation with the clinical geneticist for suspected SLOS. The consultant can then confirm the diagnosis and begin the process of identifying a laboratory to verify the diagnosis.

Management and Counseling
Management of the affected patient and genetic counseling are essential aspects of the approach to the dysmorphic patient. Children with Down syndrome have a high incidence of hypothyroidism, and children with achondroplasia have a high incidence of cervicomedullary junction constriction. Herein lies one of the many benefits of early and accurate diagnosis, because anticipatory guidance and medical monitoring of patients for syndrome-specific medical risks can prolong and improve their quality of life. When a diagnosis is made, the treating physicians can refer to published information on the natural history and management of particular syndromes through articles, genetics reference texts, online databases and, for more common disorders, general pediatric texts.

The second major benefit of an accurate diagnosis is that it provides data for appropriate recurrence risk estimates. Genetic disorders may have direct effects on only one member of the family, but the diagnosis of the condition has implications for the entire family. One or both parents may be carriers; siblings may be carriers or may wish to know their at-risk status when they reach their reproductive years. Recurrence risk provision is 1 facet of genetic counseling, which should be a component of all evaluations for families affected with birth defects or other heritable disorders (see Chapter 77).

As we understand the underlying pathophysiology of genetic disorders, particularly with respect to the developmental pathways that are disrupted by mutant genes, it will likely be possible to identify potential therapeutic targets amenable to pharmacologic intervention. Once such potential therapies are devised, the precise delineation of the syndrome responsible for the multiple congenital anomalies displayed by an individual will lead to institution of the appropriate intervention for modulating symptoms or even to ameliorate aspects of the phenotype.

Bibliography is available at Expert Consult.
Bibliography


109.1 Pathogenesis and Epidemiology

Despite advances in maternal and neonatal care, infections remain a frequent and important cause of neonatal and infant morbidity and mortality. As many as 2% of fetuses are infected in utero, and up to 10% of infants have infections in the 1st mo of life. Neonatal infections are unique in several ways:

1. Infectious agents can be transmitted from the mother to the fetus or newborn infant by diverse modes.
2. The fetus and newborn infant are less capable of responding to infection because of immunologic immaturity. Preterm infants are at particular risk.
3. Coexisting conditions often complicate the diagnosis and management of neonatal infections.
4. The clinical manifestations of newborn infections vary and include subclinical infection, mild to severe manifestations of focal or systemic infection, and, rarely, congenital syndromes resulting from in utero infection. The timing of exposure, inoculum size, immune status, and virulence of the etiologic agent influence the expression of disease.
5. Maternal infection, the source of transplacental fetal infection, is often undiagnosed during pregnancy because the mother was either asymptomatic or had nonspecific signs and symptoms at the time of acute infection.
6. A wide variety of etiologic agents infect the newborn, including bacteria, viruses, fungi, protozoa, and mycoplasmas.

Although survival has increased for immature, very-low birth-weight (VLBW) newborns, they remain in the hospital for a long time in an environment that puts them at continuous risk for acquired infections.

Bibliography is available at Expert Consult.

109.2 Modes of Transmission and Pathogenesis

PATHOGENESIS OF INTRAUTERINE INFECTION

Intrauterine infection is a result of clinical or subclinical maternal infection with a variety of agents (cytomegalovirus [CMV], Treponema pallidum, Toxoplasma gondii, rubella virus, varicella virus, parvovirus B19) and hematogenous transplacental transmission to the fetus. Transplacental infection may occur at any time during gestation, and signs and symptoms may be present at birth or may be delayed for months or years (Fig. 109-1). Infection may result in early spontaneous abortion, congenital malformation, intrauterine growth restriction, premature birth, stillbirth, acute or delayed disease in the neonatal period, or asymptomatic persistent infection with sequelae later in life. In some cases, no apparent effects are seen in the newborn infant.

The timing of infection during gestation affects the outcome. First-trimester infection may alter embryogenesis, with resulting congenital malformations (congenital rubella) (see Chapter 247). Third-trimester infection often results in active infection at the time of delivery (toxoplasmosis, syphilis) (see Chapters 290 and 218). Infections that occur late in gestation may lead to a delay in clinical manifestations until after birth (syphilis).


Maternal infection is a necessary prerequisite for transplacental infection. For some etiologic agents (rubella), maternal immunity is effective and antibody is protective for the fetus. For other agents (CMV), maternal antibody may ameliorate the outcome of infection or may have no effect (see Chapter 255). Even without maternal antibody, transplacental transmission of infection to a fetus is variable because the placenta may function as an effective barrier.

**PATHOGENESIS OF ASCENDING BACTERIAL INFECTION**

In most cases, the fetus or neonate is not exposed to potentially pathogenic bacteria until the membranes rupture and the infant passes through the birth canal and/or enters the extraterine environment. The human birth canal is colonized with aerobic and anaerobic organisms that may result in ascending amniotic infection and/or colonization of the neonate at birth. Vertical transmission of bacterial agents that infect the amniotic fluid and/or vaginal canal may occur in utero or, more commonly, during labor and/or delivery (Fig. 109-2). Chorioamnionitis results from microbial invasion of amniotic fluid, often as a result of prolonged rupture of the chorioamniotic membrane. Amniotic infection may also occur with apparently intact membranes or with a relatively brief duration of membrane rupture. The term chorioamnionitis refers to the clinical syndrome of intrauterine infection, which includes maternal fever, with or without local or systemic signs of chorioamnionitis (uterine tenderness, foul-smelling vaginal discharge/amniotic fluid, maternal leukocytosis, maternal and/or fetal tachycardia). Chorioamnionitis may also be asymptomatic, diagnosed only by amniotic fluid analysis or pathologic examination of the placenta. The rate of histologic chorioamnionitis is inversely related to gestational age at birth (Fig. 109-3) and directly related to duration of membrane rupture. Rupture of membranes for longer than 24 hr was once considered prolonged because microscopic evidence of inflammation of the membranes is uniformly present when the duration of rupture exceeds 24 hr. At 18 hr of membrane rupture, however, the incidence of early-onset disease with group B streptococcus (GBS) increases significantly; 18 hr is the appropriate cutoff for increased risk of neonatal infection.

Bacterial colonization does not always result in disease. Factors influencing which colonized infant will experience disease are not well understood but include prematurity, underlying illness, invasive procedures, inoculum size, virulence of the infecting organism, genetic predisposition, the innate immune system, host response, and transplacental maternal antibodies (Fig. 109-4). Aspiration or ingestion of bacteria in amniotic fluid may lead to congenital pneumonia or systemic infection, with manifestations becoming apparent before delivery (fetal distress, tachycardia), at delivery (failure to breathe, respiratory distress, shock), or after a latent period of a few hours (respiratory distress, shock). Aspiration or ingestion of bacteria during the birth process may lead to infection after an interval of 1-2 days.

Resuscitation at birth, particularly if it involves endotracheal intubation, insertion of an umbilical vessel catheter, or both, is associated with an increased risk of bacterial infection. Explanations include the presence of infection at the time of birth or acquisition of infection during the invasive procedures associated with resuscitation.

**PATHOGENESIS OF LATE-ONSET POSTNATAL INFECTIONS**

After birth, neonates are exposed to infectious agents in the nursery or in the community (including family). Postnatal infections may be

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**Figure 109-1** Pathogenesis of hematogenous transplacental infections. (From Klein JO, Remington JS: Current concepts of infections of the fetus and newborn infant. In Remington JS, Klein JO, editors: Infectious diseases of the fetus and newborn infant, ed 5, Philadelphia, 2002, WB Saunders.)

**Figure 109-2** Pathways of ascending or intrapartum infection.

**Figure 109-3** Histologic chorioamnionitis in liveborn preterm babies by gestational age (n = 3,928 babies). (From Lahra MM, Jeffery HE: A fetal response to chorioamnionitis is associated with early survival after preterm birth, Am J Obstet Gynecol 190:147–151, 2004.)
transmitted by direct contact with hospital personnel, the mother, or other family members; from breast milk (HIV, CMV); or from inanimate sources such as contaminated equipment. The most common source of postnatal infections in hospitalized newborns is hand contamination of healthcare personnel, underscoring the importance of handwashing.

Most cases of meningitis result from hematogenous dissemination. Less often, meningitis results from contiguous spread as a result of contamination of open neural tube defects, congenital sinus tracts, or hydrocephalus, and subdural effusions are complications of meningitis that occur more often in newborn infants than in older children.

**Bibliography** is available at Expert Consult.

**109.3 Immunity**

During the 1st 3 mo of life, the innate immune system, including phagocytes, natural killer cells, antigen presenting cells, and complement provide defense against pathogens. With advancing age and exposures, the acquired immune system develops and assumes a more prominent role in host defense. Decreased function of neutrophils and low concentrations of immunoglobulins increase the susceptibility of preterm infants to invasive infection. Group B streptococci, Escherichia coli, herpes simplex virus (HSV), CMV, varicella-zoster virus (VZV), respiratory syncytial virus (RSV), enteroviruses, and Candida species are notable pathogens in the early neonatal period.

**IMMUNOGLOBULIN**

Immunoglobulin (Ig) G is actively transported across the placenta, with concentrations in a full-term infant comparable to or higher than maternal levels, because of a combination of both acquired and neonatally produced IgG in the third trimester. In premature infants, cord IgG levels are directly proportional to gestational age; at 18-20 wk, IgG levels are <100 mg/dL and reach 400 mg/dL by 30-32 wk of gestation. Levels of maternally derived IgG fall rapidly after birth in a process termed "physiologic hypogammaglobulinemia," with notable implications for premature and small-for-gestational-age neonates, whose IgG levels are often reduced compared with term and appropriate-for-gestational-age neonates. Other classes of immunoglobulins (IgA, IgM, IgD, and IgE) are not transferred across the placenta, therefore elevated cord blood levels of IgA and IgM may be evidence of an intrauterine infection. A predisposition to Gram-negative infections in the neonate may be explained by the inequality of neonataley produced IgM to provide opsonins to these organisms. Maternal IgG is an efficient opsonin for Gram-positive organisms but is less so for Gram-negative pathogens.

Term and premature infants are able to mount immune responses to protein antigens including tetanus, diphtheria, hepatitis, and polio but are impaired in their ability to respond to polysaccharide antigens such as *Haemophilus influenzae* type b and group B streptococci. Conjugate vaccines join polysaccharide antigens to immunogenic proteins giving the appearance of a T-cell dependent antigen to the immature neonatal immune system.

**COMPLEMENT**

A fetus begins to synthesize complement components during weeks 6-14 of gestation; transplacental passage of complement from the maternal circulation does not occur. The complement system mediates bactericidal activity against certain organisms such as *E. coli* and functions as an opsonin with antibody in the phagocytosis of GBS. Full-term newborn infants have slightly diminished classical pathway complement activity and moderately diminished alternative pathway activity. Considerable variability, however, is seen in both the concentration and activity of complement components. Premature infants have lower levels of complement components and less complement activity, and have notably reduced levels of C9, important for Gram-negative bacterial lysis and assembly of the membrane attack complex. These deficiencies contribute to diminished complement-derived chemotactic activity and to a lesser ability to opsonize certain organisms in the absence of antibody.

**NEUTROPHILS**

**Neutrophil Function**

Term and late preterm neonates have impaired neutrophil function compared with that of older infants. Quantitative and qualitative deficiencies of the phagocyte system contribute to the newborn's susceptibility to infection. Neutrophil migration (chemotaxis), adhesion, aggregation, and deformability, all of which may be impaired in the neonate, may delay the response to infection. Abnormal expression of cell membrane adhesion molecules (the β, integrins and selectins) and abnormalities in the neonatal neutrophil cytoskeleton contribute to impaired chemotaxis. Impairment of the oxidative respiratory burst of neonatal neutrophils is a factor in the increased risk of sepsis, especially in preterm infants. Neutrophil granules contain enzymes; one noted protein is bactericidal/permeability-increasing protein (BPI) that binds to the endotoxin in the cell wall of Gram-negative bacteria. BPI facilitates opsonization and prevents the inflammatory response to endotoxin. BPI activity may be decreased in neonates.

**Neutrophil Number**

Neutropenia appears to be a better predictor of neonatal sepsis than leukocytosis, although neutropenic ranges differ by gestational age, mode of delivery, altitude of location of birth, and sampling methods. Neonates have a 70-80% reduction in bone marrow neutrophil stores compared to adults and therefore are impaired in their response to infectious and noninfectious stressors. Increasing neutrophil number with granulocyte colony-stimulating factors (G-CSFs) or granulocyte-macrophage colony-stimulating factors (GM-CSFs), cytokines that stimulate myeloid progenitor cells, does not appear to affect clinical outcomes. Band neutrophils constitute less than 15% in normal newborns and may increase in newborns with infection and other stress responses, such as asphyxia.

**Natural Killer Cells**

Natural killer (NK) cells are a subgroup of lymphocytes that are cytolytic against cells infected with viruses. NK cells also lyse cells coated with antibody in a process called antibody-dependent cell-mediated cytotoxicity. NK cells appear early in gestation and are present in cord
Bibliography


blood in numbers equivalent to those in adults; neonatal NK cells have an approximately 50% decrease in cytotoxic activity and antibody-dependent cell-mediated cytotoxicity in comparison with NK cells from adults.

**CYTOKINES/INFLAMMATORY MEDIATORS**

Several adverse outcomes, including brain injury, necrotizing enterocolitis, and bronchopulmonary dysplasia (BPD), may be mediated by an unbalanced cytokine (proinflammatory vs. antiinflammatory) response to infection. The release of tumor necrosis factor-α, interleukin (IL)-1 (IL-1), IL-4, IL-6, IL-8, IL-10, IL-12, platelet-activating factor, and the leukotrienes offers the potential opportunity to facilitate an early laboratory diagnosis of infection.

Functional categorization of T-helper (Th) 1 and Th2 responses is based on cytokine secretion and function. The Th1 response is directed against intracellular organisms and is relatively impaired in neonates, possibly accounting for the predisposition to severe clinical outcomes with infections with intracellular pathogens.

Innate immunity involves nonspecific cellular and humoral responses to an infectious agent without previous exposure. Recognition of pathogens is initiated by soluble components in plasma (including mannose-binding lectin) and by recognition of receptors on monocytes and other cells. Toll-like receptors play an important role in pathogen recognition.

_Bibliography is available at Expert Consult._

**109.4 Etiology of Fetal and Neonatal Infection**

A number of bacterial and nonbacterial (Table 109-1) agents may infect newborns in utero, intrapartum, or postpartum. Intrauterine transplacental infections of significance to the fetus and/or newborn include syphilis, rubella, CMV, toxoplasmosis, parvovirus B19, and varicella. Although HSV, HIV, hepatitis B virus, hepatitis C virus, and tuberculosis (TB) can each result in transplacental infection, the most common mode of transmission for these agents is intrapartum, during labor and delivery with passage through an infected birth canal (HIV, HSV, hepatitis B virus), or postpartum, from contact with an infected mother or caretaker (TB) or with infected breast milk (HIV).

Any microorganism inhabiting the genitourinary or lower gastrointestinal tract may cause intrapartum and postpartum infection. The most common bacteria are GBS and _E. coli_. The more common viruses are CMV, HSV, enteroviruses, and HIV.

Agents that commonly cause _healthcare-associated infections_ (HAIs) in the newborn include coagulase-negative staphylococci, _Gram-negative bacilli_ ( _E. coli, Klebsiella pneumoniae, Enterobacter, Pseudomonas aeruginosa_), enterococci, _Staphylococcus aureus_, and _Candida_. Viruses contributing to HAIs in the neonate include enteroviruses, CMV, hepatitis A, adenoviruses, influenza, RSV, rhinovirus, parainfluenza, HSV, and rotavirus. Community-acquired pathogens such as _Streptococcus pneumoniae_ may also cause infection in newborn infants after discharge from the hospital.

Congenital pneumonia may be caused by CMV, rubella virus, and _T. pallidum_ and, less commonly, by the other agents producing transplacental infection (Table 109-2). Microorganisms causing pneumonia acquired during labor and delivery include GBS, _Gram-negative enteric aerobes_, _Listeria monocytogenes_, _genital Mycoplasma_, _Chlamydia trachomatis_, CMV, HSV, and _Candida_ species.

Bacteria responsible for most cases of nosocomial pneumonia typically include _staphylococcal species_, _Gram-negative enteric aerobes_, and occasionally, _Pseudomonas_. Fungi are responsible for an increasing number of systemic infections, usually acquired during prolonged hospitalization of preterm neonates. Respiratory viruses cause isolated cases and outbreaks of nosocomial pneumonia. These viruses, usually endemic during the winter months and acquired from infected hospital staff or visitors to the nursery, include RSV, parainfluenza virus, influenza viruses, and adenovirus. Respiratory viruses are the single most important cause of community-acquired pneumonia and are usually contracted from infected household contacts.

The most common bacterial causes of _neonatal meningitis_ are GBS, _E. coli_, and _L. monocytogenes_. _S. pneumoniae_, other streptococci, _nontypable H. influenzae_, both coagulase-positive and coagulase-negative _staphylococci_, _Klebsiella, Enterobacter, Pseudomonas, T. pallidum_, and _Mycobacterium tuberculosis_ infection involving the central nervous system may also result in meningitis.

_Bibliography is available at Expert Consult._

**109.5 Epidemiology of Early- and Late-Onset Neonatal Infections**

The terms _early-onset infection_ and _late-onset infection_ refer to the different ages at onset of infection in the neonatal period. Although these disorders were originally divided arbitrarily into infections occurring before and after 1 wk of life, it is more useful to separate early- and late-onset infections according to peripartum pathogenesis. Early-onset infections are acquired before or during delivery (vertical mother-to-child transmission). Late-onset infections develop after delivery from organisms acquired in the hospital or the community. The age at onset depends on the timing of exposure and virulence of the infecting organism. Very-late-onset infections (onset after 1 mo of

**Table 109-1** Nonbacterial Causes of Systemic Neonatal Infections

<table>
<thead>
<tr>
<th>VIRUSES</th>
<th>MYCOPLASMA</th>
<th>FUNGI</th>
<th>PROTOZOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenovirus</td>
<td><em>Mycoplasma hominis</em></td>
<td><em>Candida species</em></td>
<td><em>Plasmodia</em></td>
</tr>
<tr>
<td>CMV</td>
<td><em>Ureaplasma urealyticum</em></td>
<td><em>Malassezia species</em></td>
<td><em>Toxoplasma gondii</em></td>
</tr>
<tr>
<td>Enteroviruses</td>
<td></td>
<td></td>
<td><em>Trypanosoma cruzi</em></td>
</tr>
<tr>
<td>Paroviruses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rubella virus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VZV</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 109-2** Etiologic Agents of Neonatal Pneumonia According to Timing of Acquisition

<table>
<thead>
<tr>
<th>TRANSPLACENTAL</th>
<th>POSTNATAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV</td>
<td>Adenovirus</td>
</tr>
<tr>
<td>HSV</td>
<td>Candida species*</td>
</tr>
<tr>
<td>Mycobacterium</td>
<td>Coagulase-negative</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>staphylococci</td>
</tr>
<tr>
<td>Rubella virus</td>
<td>CMV</td>
</tr>
<tr>
<td>Treponema pallidum</td>
<td>Enteric bacteria*</td>
</tr>
<tr>
<td>VZV</td>
<td>Enteroviruses</td>
</tr>
<tr>
<td>VZV</td>
<td>Influenza viruses A, B</td>
</tr>
<tr>
<td>RSV</td>
<td>Pseudomonas*</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>RSV</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td></td>
</tr>
</tbody>
</table>

*More likely with mechanical ventilation or indwelling catheters, or after abdominal surgery.
Bibliography
Bibliography


life) may also occur, particularly in VLBW preterm infants or term infants requiring prolonged neonatal intensive care.

The incidence of neonatal bacterial sepsis varies from 1-4/1,000 live births, with geographic variation and changes over time. Studies suggest that term male infants have a higher incidence of sepsis than term females. This sex difference is less clear in preterm low birthweight (LBW) infants. Attack rates of neonatal sepsis increase significantly in LBW infants in the presence of maternal chorioamnionitis, congenital immune defects, mutations of genes involved in the innate immune system, asplenia, galactosemia (E. coli), and malformations leading to high inocula of bacteria (obstructive uropathy).

Data from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network documented rates of early-onset sepsis among almost 400,000 live births at Network centers. The overall rate of early-onset sepsis was 0.98 cases per 1,000 live births with rates inversely related to birthweight (401-1500 g birthweight, 10.96/1000; 1501-2500 g birthweight, 1.38/1000; >2500 g birthweight, 0.57/1000) (Table 109-3).

Intrapartum antibiotics are used to reduce vertical transmission of GBS as well as to lessen neonatal morbidity after preterm rupture of membranes. With introduction of selective intrapartum antibiotic prophylaxis to prevent perinatal transmission of GBS, rates of early-onset neonatal GBS infection in the United States declined from 1.7/1,000 live births to 0.25/1,000, according to U.S. Centers for Disease Control and Prevention (CDC) surveillance data. Intrapartum chemoprophylaxis does not reduce the rates of late-onset GBS disease and has no effect on the rates of infection with non-GBS pathogens. Of concern is a possible increase in gram-negative infections (especially E. coli) in VLBW and possibly term infants in spite of a reduction in early GBS sepsis by intrapartum antibiotics.

The incidence of meningitis is 0.2-0.4/1,000 live births in newborn infants and is higher in preterm infants. Bacterial meningitis may be associated with sepsis or may occur as a local meningeal infection. Up to one-third of VLBW infants with late-onset meningitis have negative blood culture results. The discordance between results of blood and cerebrospinal fluid (CSF) cultures suggests that meningitis may be underdiagnosed among VLBW infants and emphasizes the need for culture of CSF in VLBW infants when late-onset sepsis is suspected and in all infants who have positive blood culture results.

PREMATURITY

The most important neonatal factor predisposing to infection is prematurity or LBW. Preterm LBW infants have a 3- to 10-fold higher incidence of infection than full-term normal birthweight infants. Possible explanations include: (a) maternal genital tract infection is considered to be an important cause of preterm labor, with an increased risk of vertical transmission to the newborn (Fig. 109-5); (b) the frequency of intraamniotic infection is inversely related to gestational age (see Fig. 109-3); (c) premature infants have documented immune dysfunction; and (d) premature infants often require prolonged neonatal intensive care.

The incidence of neonatal bacterial sepsis varies from 1-4/1,000 live births, with geographic variation and changes over time. Studies suggest that term male infants have a higher incidence of sepsis than term females. This sex difference is less clear in preterm low birthweight (LBW) infants. Attack rates of neonatal sepsis increase significantly in LBW infants in the presence of maternal chorioamnionitis, congenital immune defects, mutations of genes involved in the innate immune system, asplenia, galactosemia (E. coli), and malformations leading to high inocula of bacteria (obstructive uropathy).

Data from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network documented rates of early-onset sepsis among almost 400,000 live births at Network centers. The overall rate of early-onset sepsis was 0.98 cases per 1,000 live births with rates inversely related to birthweight (401-1500 g birthweight, 10.96/1000; 1501-2500 g birthweight, 1.38/1000; >2500 g birthweight, 0.57/1000) (Table 109-3).

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**Table 109-3**

<table>
<thead>
<tr>
<th>BIRTHWEIGHT (g)</th>
<th>401-1,500</th>
<th>1,501-2,500</th>
<th>&gt;2,500</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>10.96</td>
<td>1.38</td>
<td>0.57</td>
<td>0.98</td>
</tr>
<tr>
<td>GBS</td>
<td>2.08</td>
<td>0.38</td>
<td>0.35</td>
<td>0.41</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>5.09</td>
<td>0.54</td>
<td>0.07</td>
<td>0.28</td>
</tr>
</tbody>
</table>

intravenous access, endotracheal intubation, or other invasive procedures that provide a portal of entry or impair barrier and clearance mechanisms, putting them at continued risk for hospital-acquired infections.

Bibliography is available at Expert Consult.

109.6 Healthcare–Associated Infections (HAI)

HAI s are responsible for significant morbidity and late mortality in hospitalized newborns, with almost 25% of VLBW infants (<1,500 g birthweight) experiencing 1 or more nosocomial infections. The majority of HAI s occur in preterm or term infants who require intensive care. Risk factors for HAI s in these infants include prematurity, low birthweight, invasive procedures, indwelling vascular catheters, parenteral nutrition with lipid emulsions, endotracheal tubes, ventilricular shunts, alterations in the skin and/or mucous membrane barriers, frequent use of broad-spectrum antibiotics, and prolonged hospitalization. The most frequent HAI s are bloodstream infections associated with intravascular catheters and ventilator-associated pneumonia. HAI s may also occur in the absence of a catheter or ventilator. Infants receiving intensive care are at risk for community or HAI s during seasonal epidemics (RSV, influenza). Neonatal immunization during the birth hospitalization is the most reliable point of healthcare contact.

Rates of HAI s increase with decreasing birthweight and gestational age. The NICHD Neonatal Research Network has reported rates of 43% for infants weighing 401-750 g; 28% for those weighing 751-1,000 g; 15% for those weighing 1,001-1,250 g; and 7% for those weighing 1,251-1,500 g. It also reports rates of 36% for infants 22-28 wk gestational age (58% at 22 wk; 62% at 23 wk; 55% at 24 wk; 46% at 25 wk; 35% at 26 wk; 27% at 27 wk and 20% at 28 wk). The CDC National Healthcare Safety Network monitors device-associated nosocomial infection rates. Rates are inversely related to birthweight, and in level III neonatal intensive care units (NICUs), they range from 3.7 infections per 1,000 central line days for infants weighing <750 g to 2.0 infections per 1,000 central line days for those weighing >2,500 g. The widespread differences in practice regarding the inclusion of lumbar puncture (LP) in the diagnostic evaluation of an infant with suspected sepsis make it more difficult to determine rates of late-onset meningitis. The mean age at onset of the first episode of late-onset HAI sepsis occurs during 2-3 wk of life, independent of the infecting pathogen. HAI s increase the risk of adverse outcomes, including prolonged hospitalization and mortality.

Various bacterial and fungal agents colonize hospitalized infants, healthcare workers, and visitors. Pathogenic agents can be transmitted by direct contact or indirectly via contaminated equipment, intravenous fluids, medications, blood products, or enteral feedings. Colonization of the infant’s skin, umbilicus, and respiratory or gastrointestinal tract with pathogenic agents often precedes the development of infection. Antibiotic use interferes with colonization by normal flora, thereby permitting colonization with more virulent pathogens.

Coagulase-negative staphylococci are the most frequent neonatal HAI. In a cohort of 6,215 VLBW infants in the NICHD Neonatal Research Network, Gram-positive organisms were associated with 70%, Gram-negative with 18%, and fungi with 12% of episodes of late-onset sepsis; coagulase-negative staphylococci, the single most common organism, was isolated in 48% of these infections. The emergence of bacterial pathogens resistant to multiple antibiotics is a growing concern. The emergence of methicillin-resistant S. aureus, vancomycin-resistant enterococci, and multidrug-resistant Gram-negative pathogens are particularly alarming. Organisms responsible for neonatal bacterial sepsis and meningitis as well as HAI s fluctuate with antimicrobial pressure.

Viral pathogens including RSV, varicella, influenza, rotavirus, and enteroviruses may be responsible for sporadic infections or for outbreaks in the NICU. Infection prevention policies, including immunization of healthcare providers, visitors, and neonates, when feasible, are essential to prevent and/or contain nursery infection outbreaks. During clusters of infections, outbreaks, or epidemics, investigation of possible reservoirs of infection, modes of transmission, and risk factors is necessary. Identification of colonized infants and nursery personnel may be helpful. Prevention of transmission includes adherence to standard precautions with all patient contact, maintaining a manageable unit census with appropriate nurse:patient ratios, strict compliance with hand hygiene,meticulous neonatal skin care, minimizing the risk of catheter contamination, decreasing the number of venipunctures and heelsticks, reducing the duration of catheter and mechanical ventilation days, encouraging appropriate advancement of enteral feedings, providing education and feedback to nursery personnel, and ongoing monitoring and surveillance of HAI s in the NICU. Evidence-based care bundles have been developed for many procedures that may predispose a neonate to an HAI. Among those frequently practiced, intravascular central catheter insertion and care practices are frequently bundled.

Hand hygiene remains the most important and effective means of reducing HAI s. Proper hand hygiene with either soap and water or alcohol-based hand sanitizers is essential before and after each patient contact. The use of gloves does not obviate the need for hand hygiene. Skin to skin contact has proven beneficial to the neonate, however ensuring that the contact is with pathogen-free skin is essential. Ongoing education of staff regarding practices that are likely to reduce HAI s and promote active surveillance are important components of infection prevention.

Bibliography is available at Expert Consult.

109.7 Clinical Manifestations of Transplacental Intrauterine Infections

Infection with agents that cross the placenta (CMV, T. pallidum, T. gondii, rubella, parvovirus B19) may be asymptomatic at birth or may cause a spectrum of disease ranging from relatively mild symptoms to multisystem involvement with severe and life-threatening complications. For some agents, disease is characterized by chronicity, recurrence, or both, and the agent may cause ongoing injury. Clinical signs and symptoms do not help make a specific etiologic diagnosis but, rather, raise suspicion of an intrauterine infection and help distinguish these infections from acute bacterial infections that occur during labor and delivery. The following signs and symptoms are common to many of these agents (Table 109-4): intrauterine growth restriction, microcephaly or hydrocephalus, intracranial calcifications, chorioretinitis, cataracts, myocarditis, pneumonia, hepatosplenomegaly, direct hyperbilirubinemia, anemia, thrombocytopenia, hydrops fetalis, and skin manifestations. Many of these agents cause late sequelae, even if the infant is asymptomatic at birth. These adverse outcomes include sensorineural hearing loss, visual disturbances (including blindness), seizures, and neurodevelopmental abnormalities.

BACTERIAL SEPSIS

Neonates with bacterial sepsis may have either nonspecific signs and symptoms or focal signs of infection (Table 109-5), including temperature instability, hypotension, poor perfusion with pallor and mottled skin, metabolic acidosis, tachycardia or bradycardia, apnea, respiratory distress, grunting, cyanosis, irritability, lethargy, seizures, feeding intolerance, abdominal distention, jaundice, petechiae, purpura, and bleeding. Table 109-6 lists World Health Organization international criteria for bacterial sepsis. The initial manifestation may involve only limited symptomatology and only 1 system, such as apnea alone or tachypnea with retractions, or tachycardia, or the infant may present with an acute catastrophic manifestation with multiorgan dysfunction. Infants should be reevaluated over time to determine whether the symptoms have progressed from mild to severe. Later complications
Bibliography
Bibliography
of sepsis include respiratory failure, pulmonary hypertension, cardiac failure, shock, renal failure, liver dysfunction, cerebral edema or thrombosis, adrenal hemorrhage and/or insufficiency, bone marrow dysfunction (neutropenia, thrombocytopenia, anemia), and disseminated intravascular coagulopathy (DIC). A variety of noninfectious conditions can occur together with neonatal infection or can make the diagnosis of infection more difficult. Respiratory distress syndrome (RDS) secondary to surfactant deficiency can coexist with bacterial pneumonia. Because bacterial sepsis can be rapidly progressive, the physician must be alert to the signs and symptoms of possible infection and must initiate diagnostic evaluation and empirical therapy in a timely manner. The differential diagnosis of many of the signs and symptoms that suggest infection is extensive; noninfectious disorders must also be considered (Table 109-7).

### SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

The clinical manifestations of infection depend on the virulence of the infecting organism and the body's inflammatory response. The term systemic inflammatory response syndrome (SIRS) is most frequently used to describe this unique process of infection and the subsequent systemic response (see Chapters 70 and 177). In addition to infection, SIRS may result from trauma, hemorrhagic shock, other causes of systemic response (see Chapters 70 and 177). In addition to infection, SIRS is considered (Table 109-7).

### Table 109-4 Clinical Manifestations of Transplacental Infections

<table>
<thead>
<tr>
<th>MANIFESTATION</th>
<th>PATHOGEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrauterine growth restriction</td>
<td>CMV, Plasmodium, rubella, toxoplasmosis, Treponema pallidum, Trypanosoma cruzi, VZV</td>
</tr>
</tbody>
</table>

### Table 109-5 Initial Signs and Symptoms of Infection in Newborn Infants

<table>
<thead>
<tr>
<th>GENERAL</th>
<th>CARDIOVASCULAR SYSTEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever, temperature instability “Not doing well” Poor feeding Edema</td>
<td>Pallor, mottling; cold, clammy skin Tachycardia Hypotension Bradycardia</td>
</tr>
<tr>
<td>GASTROINTESTINAL SYSTEM</td>
<td>CENTRAL NERVOUS SYSTEM</td>
</tr>
<tr>
<td>Abdominal distention Diarrhea</td>
<td>Irritability, lethargy Tremors, seizures</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>Neurologically abnormal reflexes, hypotonia</td>
</tr>
<tr>
<td>RESPIRATORY SYSTEM</td>
<td>Abnormal Moro reflex</td>
</tr>
<tr>
<td>Apneic, dyspneic Tachypnea, retractions Flaring, grunting Cyanosis</td>
<td>Irregular respirations</td>
</tr>
<tr>
<td>RENAL SYSTEM</td>
<td>Full fontanel</td>
</tr>
<tr>
<td>Oliguria</td>
<td>High-pitched cry</td>
</tr>
<tr>
<td>HEMATOLOGIC SYSTEM</td>
<td>Jaundice</td>
</tr>
<tr>
<td>Petechiae, purpura</td>
<td>Splenomegaly</td>
</tr>
<tr>
<td>Bleeding</td>
<td>Pallor</td>
</tr>
</tbody>
</table>

### Table 109-6 Clinical Criteria for the Diagnosis of Sepsis in the International Setting

<table>
<thead>
<tr>
<th>System</th>
<th>Other: Temperature &gt;37.7°C (99.9°F; or feels hot) or &lt;35.5°C (95.9°F; or feels cold)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARDIOVASCULAR SYSTEM</td>
<td>Pallor, mottling; cold, clammy skin Tachycardia Hypotension Bradycardia</td>
</tr>
<tr>
<td>CENTRAL NERVOUS SYSTEM</td>
<td>Irritability, lethargy Tremors, seizures</td>
</tr>
<tr>
<td>GASTROINTESTINAL SYSTEM</td>
<td>Neurologically abnormal reflexes, hypotonia</td>
</tr>
<tr>
<td>RESPIRATORY SYSTEM</td>
<td>Abnormal Moro reflex</td>
</tr>
<tr>
<td>RENAL SYSTEM</td>
<td>Full fontanel</td>
</tr>
<tr>
<td>HEMATOLOGIC SYSTEM</td>
<td>High-pitched cry</td>
</tr>
</tbody>
</table>

Serious Systemic Illness in Newborns: Definitions of Systemic Inflammatory Response Syndrome and Sepsis in Pediatric Patients

**Table 109-7**

<table>
<thead>
<tr>
<th>CARDIAC</th>
<th>Gastrointestinal</th>
<th>HEMATOLOGIC</th>
<th>METABOLIC</th>
<th>NEUROLOGIC</th>
<th>RESPIRATORY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital: hypoplastic left heart syndrome, other structural disease, persistent pulmonary hypertension of the newborn (PPHN)</td>
<td>Necrotizing enterocolitis</td>
<td>Neonatal purpura fulminans</td>
<td>Hypoglycemia</td>
<td>Intracranial hemorrhage: spontaneous, caused by child abuse</td>
<td>Respiratory distress syndrome</td>
</tr>
<tr>
<td>Acquired: myocarditis, hypovolemic or cardiogenic shock, PPHN</td>
<td>Spontaneous gastrointestinal perforation</td>
<td>Immune-mediated thrombocytopenia</td>
<td>Adrenal disorders: Adrenal hemorrhage, adrenal insufficiency, congenital adrenal hyperplasia</td>
<td>Hypoxic-ischemic encephalopathy</td>
<td>Aspiration pneumonia: amniotic fluid, meconium, or gastric contents</td>
</tr>
<tr>
<td></td>
<td>Structural abnormalities</td>
<td>Immune-mediated neutropenia</td>
<td>Inborn errors of metabolism: Organic acidurias, lactic acidoses, urea cycle disorders, galactosemia</td>
<td>Neonatal seizures</td>
<td>Lung hypoplasia</td>
</tr>
<tr>
<td></td>
<td>Hepatic failure (inborn errors of metabolism, neonatal iron storage disease)</td>
<td>Severe anemia</td>
<td>NEUROLOGIC</td>
<td>Tracheoesophageal fistula</td>
<td>Transient tachypnea of the newborn</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Malignancies (congenital leukemia)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Langerhans cell histiocytosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hereditary clotting disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Familial hemophagocytosis syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Fever**

Only approximately 50% of infected newborn infants have a temperature higher than 37.8°C (100°F) (axillary) (see Chapters 176, 177). Fever in newborn infants does not always signify infection; it may be caused by increased ambient temperature,isolette or radiant warmer malfunction, dehydration, and central nervous system (CNS) disorders, hyperthyroidism, familial dysautonomia, or ectodermal dysplasia. A single temperature elevation is infrequently associated with infection; fever sustained over 1 hr is more likely to be caused by infection. Most febrile infected infants have additional signs compatible with infection, although a focus of infection is not always apparent. Acute febrile illnesses occurring later in the neonatal period may be caused by urinary tract infection, meningitis, pneumonia, osteomyelitis, or gastroenteritis, in addition to sepsis, thus underscoring the importance of a diagnostic evaluation that includes blood culture, urine culture, LP, and other studies as indicated. Many agents may cause these late infections, including HSV, enteroviruses, RSV, and bacterial pathogens. In premature infants, hypothermia or temperature instability requiring increasing ambient (isolette, warmer) temperatures is more likely to accompany infection.

**Rash**

Cutaneous manifestations of infection include omphalitis, cellulitis, mastitis, and subcutaneous abscesses. Ecthyma gangrenosum is indicative of infection with *Pseudomonas* species. The presence of small salmon-pink papules suggests *L. monocytogenes* infection. A vesicular rash is consistent with herpesvirus infection. The mucocutaneous lesions of *Candida albicans* are discussed elsewhere (see Chapter 234.1). Petechiae and purpura may have an infectious cause. Purple papulonodular lesions are referred to as “blueberry muffin” rash and represent dermal erythrophagocytosis. Causes include congenital viral infections (CMV, rubella, and parvovirus), congenital neoplastic disease, and Rh hemolytic disease.

**Omphalitis**

Omphalitis is a neonatal infection resulting from unhygienic care of the umbilical cord, which continues to be a problem, particularly in developing countries. The umbilical stump is colonized by bacteria from the maternal genital tract and the environment (see Chapter 105). The necrotic tissue of the umbilical cord is an excellent medium for bacterial growth. Omphalitis may remain a localized infection or may spread to the abdominal wall, peritoneum, the umbilical or portal vessels, or the liver. Abdominal wall cellulitis or necrotizing fasciitis, with associated sepsis and a high mortality rate, may develop in infants with omphalitis. Prompt diagnosis and treatment are necessary to avoid serious complications.

**Tetanus**

See also Chapter 211.

Neonatal tetanus is a serious neonatal infection in developing countries. It results from unclean delivery and unhygienic management of the umbilical cord in an infant born to a mother who has not been immunized against tetanus. The surveillance case definition of neonatal tetanus requires the ability of a newborn to suck at birth, and for the first 7 days of life, followed by an inability to suck starting between 3 and 10 days of age, difficulty swallowing, spasms, stiffness, seizures, and death. Bronchopneumonia, presumably resulting from aspiration, is a common complication and cause of death. Neonatal tetanus is a preventable disease. It can be prevented by immunizing mothers before or during pregnancy and by ensuring a clean delivery, sterile cutting of the umbilical cord and proper cord care after birth.
Pneumonia

Early signs and symptoms of pneumonia may be nonspecific, including poor feeding, lethargy, irritability, cyanosis, temperature instability, and the overall impression that the infant is not well. Respiratory symptoms of increasing severity are grunting, tachypnea, retractions, flaring of the alae nasi, cyanosis, apnea, and progressive respiratory failure. If the infant is premature, signs of progressive respiratory distress may be superimposed upon RDS or BPD. For infants on mechanical ventilation, the need to increase ventilator support may indicate infection.

Signs of pneumonia on physical examination, such as dullness to percussion, change in breath sounds, and the presence of rales or rhonchi, are very difficult to appreciate in a neonate. Radiographs of the chest may reveal new infiltrates or an effusion, but if the neonate has underlying RDS or BPD, it is very difficult to determine whether the radiographic changes represent a new process or worsening of the underlying disease.

The progression of neonatal pneumonia can be variable. Fulminant infection is most commonly associated with pyogenic organisms such as GBS (see Chapter 184). Onset may occur during the 1st hours or days of life, with the infant often manifesting rapidly progressive circulatory collapse and respiratory failure. With early-onset pneumonia, the clinical course and radiographs of the chest may be indistinguishable from those with severe RDS.

In contrast to the rapid progression of pneumonia caused by pyogenic organisms, an indolent course may be seen in nonbacterial infection. The onset can be preceded by upper respiratory tract symptoms or conjunctivitis. The infant may demonstrate a nonproductive cough, and the degree of respiratory compromise is variable. Fever is usually absent, and radiographic examination of the chest shows focal or diffuse interstitial pneumonitis. Infection is generally caused by C. trachomatis, CMV, Ureaplasma urealyticum, or 1 of the respiratory viruses. Rhinovirus has been reported to cause severe respiratory compromise in infants, particularly those who are preterm. Although Pneumocystis (carinii) jiroveci was implicated in the original description of this syndrome, its etiologic role is now in doubt, except in newborns infected with HIV.

Bibliography is available at Expert Consult.

109.8 Intrapartum and Peripartum Infections

The maternal history provides important information about maternal exposures to infectious diseases, bacterial colonization, immunity (natural and acquired), and obstetric risk factors (prematurity, prolonged ruptured membranes, maternal chorioamnionitis).

Sexually transmitted infections (STIs) acquired by a pregnant woman are of particular concern to the fetus and newborn because of the potential for intrauterine or perinatal transmission. All pregnant women and their partners should be queried about a history of STIs. Women should also be counseled about the need for timely diagnosis and therapy for infections during pregnancy. The CDC recommends the following screening tests and treatment when indicated:

1. All pregnant women should be offered voluntary and confidential HIV testing at the first prenatal visit, as early in pregnancy as possible. HIV screening should be part of routine prenatal testing, unless the mother declines testing (opt-out screening). For women at high risk of infection during pregnancy (multiple sexual partners or STIs during pregnancy, intravenous drug use, HIV-infected partners), repeat testing in the 3rd trimester is recommended. Rapid HIV screening is indicated for any women who presents in labor with an undocumented HIV status, unless she declines testing.

2. A serologic test for syphilis should be performed on all pregnant women at the first prenatal visit. Repeat screenings early in the 3rd trimester and again at delivery are recommended for women in whom syphilis test results in the 1st trimester were positive and for those at high risk for infection during pregnancy. Infants should not be discharged from the hospital unless the syphilis status of the mother has been determined at least once during pregnancy and preferably again at delivery.

3. Serologic testing for hepatitis B surface antigen (HBsAg) should be performed at the first prenatal visit, even if the woman has been previously vaccinated or tested. Women who were not screened prenatally, those who are at high risk for infection (multiple sexual partners, intravenous drug use, HBsAg-positive sex partner) and those with clinical hepatitis should be retested at the time of delivery.

4. A maternal genital culture for C. trachomatis should be performed at the first prenatal visit. Young women (<25 yr) and those at increased risk for infection (new or multiple partners during pregnancy) should be retested during the 3rd trimester.

5. A maternal culture for Neisseria gonorrhoeae should be performed at the first prenatal visit. Those at high risk for infection should be retested in the 3rd trimester.

6. All pregnant women at high risk for hepatitis C infection (intravenous drug use, blood transfusion or organ transplantation before 1992) should be screened for hepatitis C antibodies at the first prenatal visit.

7. Evidence does not support routine testing for bacterial vaginosis in pregnancy. For asymptomatic women at high risk for preterm delivery, testing may be considered. Symptomatic women should be tested and treated.

8. The CDC recommends universal screening for rectovaginal GBS colonization of all pregnant women at 35–37 wk gestation, and a screening-based approach to selective intrapartum antibiotic prophylaxis against GBS (Table 109-9 and Figs. 109-6 and 109-7; Chapter 184). Figure 109-8 shows the approach to the infant born after intrapartum prophylaxis.

Suspected Intrauterine Infection

The acronym TORCH refers to toxoplasmosis, other agents (syphilis, varicella, parvovirus B19, HIV), rubella, CMV, and HSV. Although the acronym may be helpful in remembering some of the etiologic agents of intrauterine infection, the TORCH battery of serologic tests has a poor diagnostic yield. Instead, individual diagnostic studies should be selected for each etiologic agent under consideration. CMV and HSV require culture or polymerase chain reaction (PCR) methods; toxoplasmosis is diagnosed by serologic tests and PCR, whereas syphilis and rubella are diagnosed by serologic methods. Furthermore, reaching a definitive diagnosis of a congenital infection and dating the infection may require assessment of maternal diagnostic testing. Neonatal antibody titers are often difficult to interpret because (1) IgG is acquired from the mother by transplacental passage and (2) determination of neonatal IgM titers to specific pathogens is technically difficult to perform and is not universally available. IgM titers to specific pathogens have high specificity but only moderate sensitivity; they should not be used to preclude infection. Paired maternal and fetal/neonatal IgG titers showing higher newborn IgG levels or rising IgG titers during infancy may be used to diagnose some congenital infections (syphilis). Total cord blood IgM or IgA (neither is actively transported across the placenta to the fetus) and the presence of IgM–rheumatoid factor in neonatal serum are nonspecific tests for intrauterine infection.

If the likelihood of maternal infection with a known teratogenic agent is high, fetal ultrasound examination is recommended. If the examination demonstrates either a physical abnormality or delayed growth for gestational age, examination of a fetal blood sample may be warranted. Cordocentesis can provide a sufficient sample for both total and pathogen-specific IgM assays, for PCR, or for culture. The total IgM value is important because the normal fetal IgM level is <5 mg/dL. Any elevation in total IgM may indicate an underlying fetal infection. Specific IgM antibody tests are available for CMV, T. pallidum, parvovirus B19, and toxoplasmosis. IgM tests are useful when the
Bibliography
Algorithm for GBS intrapartum prophylaxis for women with preterm labor (PTL)

1. Patient with signs and symptoms of preterm labor
2. Obtain vaginal-rectal swab for GBS culture* and start GBS prophylaxis
3. Patient entering true labor?†
   - Yes: Continue GBS prophylaxis until delivery‡
   - No: Discontinue GBS prophylaxis
4. Obtain GBS culture results
   - Positive: GBS prophylaxis at onset of true labor
   - Negative: Not available prior to labor onset and patient still preterm
   - No GBS prophylaxis§: Repeat vaginal-rectal culture if patient reaches 35-37 weeks' gestation and has not yet delivered¶

Algorithm for GBS intrapartum prophylaxis for women with preterm premature rupture of membranes (pPROM)

1. Obtain vaginal-rectal swab for GBS culture* and start antibiotics for latency† OR GBS prophylaxis
2. Patient entering labor?
   - Yes: Continue antibiotics per standard of care if receiving for latency; OR continue antibiotics for 48 hours‡ if receiving for GBS prophylaxis
   - No: Obtain GBS culture results
3. Positive: GBS prophylaxis at onset of labor
4. Negative: Not available prior to labor onset
5. No GBS prophylaxis§: Repeat vaginal-rectal culture if patient reaches 35-37 weeks' gestation and has not yet delivered¶

* If patient has undergone vaginal-rectal GBS culture within the preceding 5 weeks, the results of that culture should guide management. GBS colonized women should receive intrapartum antibiotic prophylaxis. No antibiotics are indicated for GBS prophylaxis if a vaginal-rectal screen within 5 weeks was negative.
† Patient should be regularly assessed for progression to true labor; if the patient is considered not to be in true labor, discontinue GBS prophylaxis.
‡ If GBS culture results become available before delivery and are negative, then discontinue GBS prophylaxis.
§ Unless subsequent GBS culture before delivery is positive.
¶ A negative GBS screen is considered valid for 5 weeks. If a patient with a history of PTL is re-admitted with signs and symptoms of PTL and had a negative GBS screen >5 weeks prior, she should be re-screened and managed according to this algorithm at that time.

Results are strongly positive; however a negative pathogen-specific IgM result does not rule out that pathogen as a cause of fetopathy. If maternal serologic studies point to a specific pathogen, it is sometimes possible to detect the organism in amniotic fluid or fetal blood (culture, PCR). Amniocentesis can be performed and the fluid sent for analysis. The presence of CMV, Toxoplasma, or parvovirus in amniotic fluid indicates that the fetus is infected and at high risk, but it does not always mean that the fetus will have severe sequelae. In contrast, HSV and VZV are rarely isolated from amniotic fluid samples. Parvovirus does not grow in the cell cultures commonly available in the virology...
Algorithm for secondary prevention of early-onset GBS disease among newborns

1. Signs of neonatal sepsis?  
   - Yes: Full diagnostic evaluation*  
   - Antibiotic therapy†  
   - No:
     - Maternal chorioamnionitis?§  
       - Yes: Limited evaluation¶  
       - Antibiotic therapy†  
       - No:
         - GBS prophylaxis indicated for mother?**  
           - Yes: Observation for ≥48 hours††‡‡  
           - No:
             - Mother received ≥4 hours of penicillin, ampicillin or cefazolin IV?  
               - Yes: Observation for ≥48 hours††‡‡  
               - No:
                 - ≥37 weeks AND duration of membrane rupture <18 hours?  
                   - Yes: Observation for ≥48 hours††‡‡  
                   - No:
                     - Either <37 weeks OR duration of membrane rupture ≥18 hours?  
                       - Yes: Limited evaluation††  
                       - No: Observation for ≥48 hours††‡‡

* Full diagnostic evaluation includes a blood culture, a complete blood count (CBC) including white blood cell differential and platelet counts, chest radiograph (if respiratory abnormalities are present), and LP (if patient stable enough to tolerate procedure and sepsis is suspected).
† Antibiotic therapy should be directed toward the most common causes of neonatal sepsis including intravenous ampicillin for GBS and coverage for other organisms (including Escherichia coli and other gram-negative pathogens), and should take into account local antibiotic resistance patterns.
¶ Consultation with obstetric providers is important to determine the level of clinical suspicion for chorioamnionitis. Chorioamnionitis is diagnosed clinically and some of the signs are nonspecific.
‡ Limited evaluation includes blood culture (at birth), and CBC with differential and platelets (at birth and/or at 6-12 hours of life).
** GBS prophylaxis indicated in one or more of the following: (1) mother GBS positive within preceding 5 weeks, (2) GBS status unknown with one or more intrapartum risk factors including <37 weeks’ gestation, ROM ≥ 18 hours or T ≥ 100.4°F (38.0°C), (3) GBS bacteriuria during current pregnancy, (4) history of a previous infant with GBS disease.
†† If signs of sepsis develop, a full diagnostic evaluation should be done and antibiotic therapy initiated.
‡‡ If ≥37 weeks’ gestation, observation may occur at home after 24 hours if other discharge criteria have been met, there is ready access to medical care, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions is not met, the infant should be observed in the hospital for at least 48 hours and until discharge criteria are achieved.
¶¶ Some experts recommend a CBC with differential and platelets at 6-12 hours of age.

**Figure 109-8** Algorithm for secondary prevention of early-onset GBS disease among newborns. (From Verani J, McGee L, Schrag S: Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010, MMWR Recomm Rep 59(RR-10):1–36, 2010.)

**Table 109-9** Indications for Intrapartum Antibiotic Prophylaxis to Prevent Early-Onset GBS Disease

<table>
<thead>
<tr>
<th>INTRAPARTUM GBS PROPHYLAXIS INDICATED</th>
<th>INTRAPARTUM GBS PROPHYLAXIS NOT INDICATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous infant with invasive GBS disease</td>
<td>Colonization with GBS during a previous pregnancy (unless an indication for GBS prophylaxis is present for current pregnancy)</td>
</tr>
<tr>
<td>GBS bacteriuria during any trimester of the current pregnancy</td>
<td>GBS bacteriuria during previous pregnancy (unless another indication for GBS prophylaxis is present for current pregnancy)</td>
</tr>
<tr>
<td>Positive GBS screening culture during current pregnancy (unless a cesarean delivery is performed before onset of labor or amniotic membrane rupture)</td>
<td>Cesarean delivery before onset of labor or amniotic membrane rupture, regardless of GBS colonization status or gestational age</td>
</tr>
</tbody>
</table>
| Unknown GBS status at the onset of labor (culture not done, incomplete, or results unknown) and any of the following: Delivery at <37 weeks’ gestation*  
  Amniotic membrane rupture ≥18 hr  
  Intrapartum temperature ≥38.0°C (100.4°F)†  
  Intrapartum NAAT‡ positive for GBS | Negative vaginal and rectal GBS screening culture in late gestation during the current pregnancy, regardless of intrapartum risk factors |

*Recommendations for the use of intrapartum antibiotics for prevention of early-onset GBS disease in the setting of threatened preterm delivery are presented in Figures 109-7 and 109-8.
†If amnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent known to be active against GBS should replace GBS prophylaxis.
‡If intrapartum NAAT is negative for GBS but any other intrapartum risk factor (delivery at <37 weeks’ gestation, amniotic membrane rupture ≥18 hr, or temperature ≥38.0°C[100.4°F]) is present, then intrapartum antibiotic prophylaxis is indicated.
‡‡GBS, group B streptococcus; NAAT, nucleic acid amplification test.
laboratory. An IgM response is dependent on the timing of the primary infection in relationship to specimen acquisition. When fetal parvovirus infection is suspected, testing of fetal blood or amniotic fluid by PCR is recommended in addition to testing for a specific IgM response in the fetus. PCR may also be used for the diagnosis of toxoplasmosis, CMV, HSV, rubella, and syphilis.

Neonatal infections with CMV, Toxoplasma, rubella, HSV, and syphilis present a diagnostic dilemma because (1) their clinical features overlap and may initially be indistinguishable; (2) disease may be unapparent; (3) maternal infection is often asymptomatic; (4) special laboratory studies may be needed; and (5) appropriate management of toxoplasmosis, syphilis, CMV, and HSV, is predicated on an accurate diagnosis. Common shared features that should suggest the diagnosis of an intrauterine infection include intrauterine growth restriction, hematologic involvement (anemia, neutropenia, thrombocytopenia, petechiae, purpura), ocular signs (chorioretinitis, cataracts, keratoconjunctivitis, glaucoma, microphthalmos), CNS involvement (microcephaly, aseptic meningitis, hydrocephaly, intracranial calcifications), other organ system involvement (pneumonia, myocarditis, nephritis, hepatitis with hepatosplenomegaly, jaundice), and nonimmune hydrops. Diagnostic studies in newborns with suspected intrauterine infections should test for each potential etiology individually with acute and convalescent titers. Hepatic dysfunction, with abnormal liver functions tests, may be seen in infants with CMV, HSV, and enteroviral infections. Neonatal HSV disease should be confirmed by PCR identification of HSV from the CSF and blood. Given that approximately 30% of infants infected with HSV present with isolated mucocutaneous manifestations, swabs of any skin lesions, the conjunctiva, and oral and rectal mucosa should also be performed in all infants with suspected HSV disease. Enzyme Linked Virus Inducible System (ELVIS), a simple, 24-hr cell culture test for detecting HSV, compares favorably to standard cell culture sensitivity. HIV PCR testing should be routinely performed on infants with suspected or confirmed congenital infections that may have been cotransmitted with another etiology (HSV, toxoplasmosis). Although exposure cannot be differentiated from infection until 4-6 mo of age, empiric treatment and monitoring may prevent the sequelae of a vertically transmitted HIV infection. Maternal HIV testing is essential to provide guidance regarding breastfeeding practices to the mother of a potentially exposed/infected neonate.

**Bibliography is available at Expert Consult.**

### 109.9 Suspected Bacterial or Fungal Infections

Bacterial and fungal infections are diagnosed by isolating the etiologic agent from a normally sterile body site (blood, CSF, urine, joint fluid). Obtaining 2 blood culture specimens by venipuncture from different sites avoids confusion caused by skin contamination and increases the likelihood of bacterial detection. Samples for blood culture should be obtained from an umbilical catheter only at the time of initial insertion. A peripheral venous sample should also be obtained when blood is drawn for culture from central venous catheters or from peripherally inserted central catheters (PICC lines). Although blood cultures are usually the basis for a diagnosis of bacterial infection, the bacteremic phase of the illness may be missed by poor timing of cultures or inadequate blood volume sampled. Low-level bacteremia (<10 colony-forming units/mL) has been observed in some infants from birth to 2 mo of age with positive culture results, however 1-2 mL of blood should increase microorganism recovery in the face of low-colony-count sepsis. Automated blood culture systems (BACTEC, Becton Dickinson; Bact/Alert, Organon Teknika), which continuously monitor blood cultures by checking each bottle every few minutes, result in earlier detection of bacterial growth. After positive signaling in the automated system, the specific pathogen is identified by biochemical tests. PCR technology is emerging for more rapid accurate identification of a number of viral and bacterial agents. Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry may assist with early identification of pathogens from blood cultures, optimizing empirical antibiotic therapy in the setting of bloodstream infections. This emerging technique is superior to immunological methods of detection and more rapid than culture, especially of slow-growing organisms.

Documentation of a positive blood culture result is the first diagnostic criterion that must be met for sepsis (Table 109-10). However, some neonates with bacterial infection may have negative blood culture results (“clinical infection” or “clinical sepsis”), and other approaches to identification of etiology are needed. Commonly used diagnostic tests include the total WBC count and differential count and the ratio of neutrophils to lymphocytes.

<table>
<thead>
<tr>
<th>Table 109-10</th>
<th>Evaluation of a Newborn for Infection or Sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HISTORY (SPECIFIC RISK FACTORS)</strong></td>
<td>Maternal infection during gestation or at parturition (type and duration of antimicrobial therapy):</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td></td>
<td>Chorioamnionitis</td>
</tr>
<tr>
<td></td>
<td>Maternal colonization with group B streptococci, N. gonorrhoeae, herpes simplex</td>
</tr>
<tr>
<td></td>
<td>Gestational age/birthweight</td>
</tr>
<tr>
<td></td>
<td>Multiple birth</td>
</tr>
<tr>
<td></td>
<td>Duration of membrane rupture</td>
</tr>
<tr>
<td></td>
<td>Complicated delivery</td>
</tr>
<tr>
<td></td>
<td>Fetal tachycardia (distress)</td>
</tr>
<tr>
<td></td>
<td>Age at onset (in utero, birth, early postnatal, late)</td>
</tr>
<tr>
<td></td>
<td>Location at onset (hospital, community)</td>
</tr>
<tr>
<td></td>
<td>Medical intervention:</td>
</tr>
<tr>
<td></td>
<td>Vascular access</td>
</tr>
<tr>
<td></td>
<td>Endotracheal intubation</td>
</tr>
<tr>
<td></td>
<td>Parenteral nutrition</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
</tr>
<tr>
<td><strong>EVIDENCE OF OTHER DISEASES</strong>*</td>
<td>Congenital malformations (heart disease, neural tube defect)</td>
</tr>
<tr>
<td></td>
<td>Respiratory tract disease (respiratory distress syndrome, aspiration)</td>
</tr>
<tr>
<td></td>
<td>Necrotizing enterocolitis</td>
</tr>
<tr>
<td></td>
<td>Metabolic disease, e.g., galactosemia</td>
</tr>
<tr>
<td><strong>EVIDENCE OF FOCAL OR SYSTEMIC DISEASE</strong></td>
<td>General appearance, neurologic status</td>
</tr>
<tr>
<td></td>
<td>Abnormal vital signs</td>
</tr>
<tr>
<td></td>
<td>Organ system disease</td>
</tr>
<tr>
<td></td>
<td>Feeding, stools, urine output, extremity movement</td>
</tr>
<tr>
<td><strong>LABORATORY STUDIES</strong></td>
<td>Evidence of Infection</td>
</tr>
<tr>
<td></td>
<td>Culture from a normally sterile site (blood, CSF, other)</td>
</tr>
<tr>
<td></td>
<td>Demonstration of a microorganism in tissue or fluid</td>
</tr>
<tr>
<td></td>
<td>Molecular detection (blood, urine, CSF)</td>
</tr>
<tr>
<td></td>
<td>Maternal or neonatal serology (syphilis, toxoplasmosis)</td>
</tr>
<tr>
<td></td>
<td>Autopsy</td>
</tr>
<tr>
<td></td>
<td>Evidence of Inflammation</td>
</tr>
<tr>
<td></td>
<td>Leukocytosis, increased immature/total neutrophil count ratio</td>
</tr>
<tr>
<td></td>
<td>Acute-phase reactants: C-reactive protein, erythrocyte sedimentation rate</td>
</tr>
<tr>
<td></td>
<td>Cytokines: interleukin-6, interleukin-B, tumor necrosis factor</td>
</tr>
<tr>
<td></td>
<td>Pleocytosis in CSF or sylvial or pleural fluid</td>
</tr>
<tr>
<td></td>
<td>Disseminated intravascular coagulation: fibrin degradation products, D-dimer</td>
</tr>
<tr>
<td></td>
<td>Evidence of Multiorgan System Disease</td>
</tr>
<tr>
<td></td>
<td>Metabolic acidosis: pH, P CO2</td>
</tr>
<tr>
<td></td>
<td>Pulmonary function: P O2, P CO2</td>
</tr>
<tr>
<td></td>
<td>Renal function: blood urea nitrogen, creatinine</td>
</tr>
<tr>
<td></td>
<td>Hepatic injury/function: bilirubin, alanine aminotransferase, aspartate aminotransferase, ammonia, prothrombin time, partial thromboplastin time</td>
</tr>
<tr>
<td></td>
<td>Bone marrow function: neutropenia, anemia, thrombocytopenia</td>
</tr>
</tbody>
</table>

*Diseases that increase the risk of infection or may overlap with signs of sepsis.*
**Bibliography**


of immature to total neutrophils. Although both have limitations in sensitivity and specificity, an immature:total neutrophil ratio of ≥0.2 suggests bacterial infection. Neutropenia is more common than neutrophilia in severe neonatal sepsis, but neutropenia also occurs in association with maternal hypertension, preeclampsia, and intrauterine growth restriction. Thrombocytopenia is a nonspecific indicator of infection and in some situations may suggest a fungal etiology. Tests to demonstrate an inflammatory response include determinations of C-reactive protein, procalcitonin, haptoglobin, fibrinogen, proteomic markers in amniotic fluid, inflammatory cytokines (including IL-6, IL-8, and tumor necrosis factor-α), and cell surface markers. Some of these modalities are readily available in clinical laboratories, while others are limited to research settings. Some investigators have attempted to develop and validate “sepsis scores” by incorporating different combinations of inflammatory response parameters and clinical presentation, but a single score has not proven to be consistently reliable.

When the clinical findings suggest an acute infection and the site of infection is unclear, LP with culture of CSF, urine culture, and a chest radiograph should be considered in addition to blood cultures. Urine should be collected by catheterization or suprapubic aspiration to avoid contamination. Urine culture for bacteria can be omitted in suspected early-onset infections because hematogenous spread to the urinary tract is rare in the 1st few days of life. Examination of the buffy coat with Gram or methylene blue stain may demonstrate intracellular pathogens. Demonstration of bacteria and inflammatory cells in Gram-stained gastric aspirates on the 1st day of life may reflect maternal amnionitis, which is a risk factor for early-onset infection. Stains of endotracheal secretions in infants with early-onset pneumonia may demonstrate intracellular bacteria, and cultures may reveal either pathogens or upper respiratory tract flora. However, rapid colonization of the neonatal respiratory tract after intubation may make tracheal aspirates less useful as a diagnostic modality for infection. Careful pathologic and microbiologic examination of the placenta can be helpful in the diagnosis of both chronic and acute intrauterine infections.

Diagnostic evaluation (including blood culture) is indicated for asymptomatic infants born to mothers with chorioamnionitis. The probability of neonatal infection correlates with the degree of prematurity and bacterial contamination of the amniotic fluid. Some experts recommend presumptive treatment with antibiotics, usually ampicillin and gentamicin or cefotaxime. In contrast, all symptomatic infants should be treated with antibiotics, usually ampicillin and gentamicin, or cefotaxime, after blood cultures are obtained. There is controversy over whether a LP is necessary for all term infants with suspected early-onset sepsis. Signs and symptoms of sepsis may be nonspecific and may include temperature instability, decreased responsiveness, respiratory distress, poor feeding, enesis, and diarrhea. Findings commonly observed in older infants with bacterial meningitis including stiff neck, bulging fontanel, convulsions, and opisthotonus, are rare in neonates with bacterial meningitis, making identification of neonatal meningitis from a clinical examination challenging. If a pathogen is isolated from blood culture or if an infant develops signs and symptoms consistent with sepsis, a LP is indicated. Some organisms such as GBS may be present only in the CSF and not in the blood at the time of an early onset sepsis evaluation. If the mother has been treated with antibiotics for chorioamnionitis, the newborn’s blood culture result may be negative, and the clinician must rely on clinical observation and other laboratory tests (Table 109-11).

PNEUMONIA AND PNEUMONITIS

The differential diagnosis of pneumonitis in neonates is broad and includes RDS, meconium aspiration syndrome, persistent pulmonary hypertension, diaphragmatic hernia, transient tachypnea of the newborn, congenital heart disease, and BPD. The diagnosis of infectious pneumonia in a neonate is usually presumptive; microbiologic proof of infection is generally lacking because lung tissue is not easily cultured. CDC definitions of ventilator-associated pneumonia were developed to assist with monitoring of this condition in premature and low birthweight infants. Bacteriologic cultures of tracheal aspires often reflect upper respiratory tract commensal organisms and usually have no etiologic significance. Culture of fluid obtained by bronchoalveolar lavage in a neonate is unreliable because the small bronchoscopes used in neonates cannot be protected from contamination as they are introduced into the distal airways. Short of tissue obtained by lung biopsy, the only reliable bacteriologic cultures are those performed on specimens obtained from blood or pleural fluid. Unfortunately, blood culture results are usually negative in the presence of a clinical pneumonia, and sufficient pleural fluid for culture is rarely present. Culture of pleural fluid obtained from a chest tube is not considered to be from a sterile site unless the specimen was obtained at the time of thoracostomy.

Cultures of respiratory secretions for U. urealyticum and other genital Mycoplasma species are of little value because neonates are often colonized with these agents as a result of ingestion of colonized secretions from the maternal genital tract. Neonatal C. trachomatis may be manifest by an elevated antichlamydial IgM titer, peripheral eosinophilia and elevated serum immunoglobulin levels as well as identification of the organism from the maternal genital tract. Giemsa-stained smears of conjunctivae or nasopharyngeal mucosa may reveal inclusion bodies confirming the diagnosis. Assessments of neonates for the presence of respiratory viruses by molecular analyses of nasopharyngeal specimens and enteroviruses by molecular analysis of blood and CSF may be beneficial during endemic seasons. Other tests of potential value in evaluating neonates with possible infectious pneumonitis are discussed under diagnosis of infections (see Chapter 109.7).

MENINGITIS

The diagnosis of meningitis is confirmed by examination of CSF and identification of a bacterium, virus, or fungus by culture, antigen, or molecular analysis. The importance of the LP as part of the diagnostic evaluation of the neonate with suspected sepsis has been the subject of debate and clinical practice varies. For term infants with suspected early-onset sepsis, many clinicians routinely obtain blood cultures and a complete blood count, because the etiology of 70-85% of term neonates with bacterial meningitis may be demonstrated by blood culture. Examination and culture of CSF may subsequently be undertaken in term infants with symptoms and/or bacteremia. Many clinicians defer the LP in severely ill infants with suspected early-onset infection because of the fear of respiratory and/or cardiovascular compromise associated with positioning for the procedure. In these situations, blood cultures should be performed and treatment initiated for presumed meningitis until an LP can be safely performed. In some situations, pretreatment with antibiotics makes interpretation of the LP results difficult and some experts would empirically treat the neonate for presumptive meningitis, using higher meningitic doses of antimicrobials and for an extended duration based on the suspected pathogen(s).

Term uninfected infants in the 1st wk of life may have the following CSF findings: protein 84 ± 45 mg/dL, glucose 46 ± 10 mg/dL, and leukocyte count 11 ± 10/mm³ with the 90th percentile for leukocyte count being 22/mm³. The proportion of polymorphonuclear leukocytes is 2.2 ± 3.8% with the 90th percentile being 6%. A cross-sectional study that included neonates ≤56 days of age (15% premature) during 2005-2007 who underwent LP as part of a sepsis evaluation without clinical pneumonia and sufficient pleural fluid for culture. Unfortu-

Chapter 109  •  Infections of the Neonatal Infant 921
Part XII

Culture

When clinically feasible

MHC II

CD64

Elevated for 24

Culture

Thrombocytopenia and

Neutropenia

CSF WBC

Uninfected neonates mean 10 cells/mm³.

CSF protein

Culture-Based and Non–Culture-Based Diagnostics for Neonatal Sepsis

After 24


class II; NPV, negative predictive value; TNF, tumor necrosis factor; WBC, white blood cell count.

Bibliography is available at Expert Consult.

but may be <100 in infants with neutropenia or when the CSF is obtained early in the disease course. Microorganisms are recovered from most patients who have not been pretreated with antibiotics. Bacterial organisms have also been noted microscopically and grown from CSF without an abnormal number of WBCs (<25) or with a normal protein level (<200 mg/dL), thus underscoring the importance of performing a culture and Gram stain on all CSF specimens. Contamination of CSF by bacteremia after traumatic LP may occur rarely. Culture-negative meningitis may be seen with antibiotic pretreatment, a brain abscess, or infection with Mycobacterium hominis, U. urealyticum, Bacteroides fragilis, enterovirus, or HSV. Use of PCR has improved the ability to detect pathogens rapidly in CSF, especially enteroviruses and HSV. Head ultrasonography or, more often, CT with contrast enhancement may be helpful in diagnosing ventriculitis and brain abscess.

Bibliography is available at Expert Consult.

109.10 Management

EMPIRIC THERAPY

The optimal course of management of neonates with a suspected bacterial infection is determined by the age of the neonate, the prenatal and postnatal environment, and epidemiology (Table 109-12). Once appropriate culture specimens have been obtained intravenous or, less often, intramuscular antibiotic therapy should be instituted immediately. Although it is preferable to have specimens obtained prior to the initiation of antimicrobial therapy to optimize recovery of bacterial organisms, antimicrobial therapy administration should be delayed for specimen collection in clinically ill neonates. Initial empirical treatment of early-onset bacterial infections should consist of ampicillin and an aminoglycoside (usually gentamicin), or cefotaxime. HAIs acquired in a NICU are more likely to be caused by staphylococci, various Enterobacteriaceae, Pseudomonas species, or Candida species. Thus, an antistaphylococcal drug (oxacillin or nafcillin for S. aureus or, more often, vancomycin for coagulase-negative staphylococci or methicillin-resistant S. aureus) should be substituted for ampicillin in a previously hospitalized neonate. A history of recent antimicrobial therapy or the presence of antibiotic-resistant infections in the NICU suggests the need for modification of empiric antimicrobial choices. When the history or the presence of necrotic skin lesions suggests Pseudomonas infection, initial therapy should consist of antipseudomonal agent, such as piperacillin, ticarcillin, meropenem, or ceftazidime, and an aminoglycoside. Fungal infections, including candidiasis or aspergillosis, should also be considered when necrotic skin lesions at former sites of adhesive tape are observed. These require immediate surgical intervention as well as antifungal therapy.

Involvement of a pharmacist with expertise in neonatal infections and/or use of a guide containing neonatal dosing by weight and

Table 109-11

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>PARAMETER</th>
<th>OPTIMAL TIMING, VOLUME OF SPECIMEN, ROUTINE/INVESTIGATIONAL</th>
<th>APPLICABILITY FOR NEONATAL SEPSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture-based</td>
<td>Blood</td>
<td>&gt;1 mL of whole blood ROUTINE*</td>
<td>Gold standard for bacteremia</td>
</tr>
<tr>
<td></td>
<td>Cerebrospinal fluid (CSF)</td>
<td>When clinically feasible ROUTINE</td>
<td>Optimize antimicrobial therapy</td>
</tr>
<tr>
<td></td>
<td>Urine</td>
<td>&gt;72 hr of life ROUTINE</td>
<td>Not useful for EOS; potential benefits for LOS</td>
</tr>
<tr>
<td></td>
<td>Tracheal aspirate</td>
<td>ROUTINE</td>
<td>Usually reflects colonization</td>
</tr>
<tr>
<td>Non–culture-based</td>
<td>Immune function</td>
<td>MHC II</td>
<td>Both decreased in choioamnionitis and sepsis Neutropenia better predictor for sepsis than leukocytosis</td>
</tr>
<tr>
<td>Neutrophil indices</td>
<td>Absolute neutrophil count</td>
<td>INVESTIGATIONAL1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Absolute immature neutrophil count</td>
<td>INVESTIGATIONAL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neutrophil markers</td>
<td>CD64</td>
<td>Cut points between 2.38–3.62 optimal sensitivity, specificity and NPV for EOS</td>
</tr>
<tr>
<td></td>
<td>Platelet count</td>
<td>Thrombocytopenia and thrombocytosis</td>
<td>Thrombocytopenia associated with fungal infection</td>
</tr>
<tr>
<td></td>
<td>CSF cell count</td>
<td>CSF WBC</td>
<td>Does not predict culture-proven meningitis</td>
</tr>
<tr>
<td></td>
<td>CSF chemistries</td>
<td>CSF protein</td>
<td>Elevated in fungal meningitis</td>
</tr>
<tr>
<td></td>
<td>Acute phase reactants</td>
<td>CRP</td>
<td>Low glucose specific for bacterial meningitis</td>
</tr>
<tr>
<td></td>
<td>Sepsis panels/scores</td>
<td>Procalcitonin</td>
<td>Good NPV</td>
</tr>
</tbody>
</table>

Note: ROUTINE refers to an assay or parameter that is routinely available and widely used.

*ROUTINE refers to an assay or parameter that is undergoing evaluation for clinical use and applicability.

CRP, C-reactive protein; CSF, cerebrospinal fluid; EOS, early-onset sepsis; GA, gestational age; LOS, late-onset sepsis; MHC II, major histocompatibility complex class II; NPV, negative predictive value; TNF, tumor necrosis factor; WBC, white blood cell count.

Bibliography
Management and Prevention of Neonatal Sepsis

Table 109-12  Management and Prevention of Neonatal Sepsis

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>THERAPY</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empiric management</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early-onset sepsis</td>
<td>Ampicillin + aminoglycoside. 10 days for bacteremia; 14 days for GBS and uncomplicated meningitis; extend to 21-28 days for complicated infections.</td>
<td>Consider a third-generation cephalosporin (cefotaxime preferred) or carbapenem for meningitis. Tailor therapy to pathogen. Consider discontinuation of therapy if pathogen not isolated.</td>
</tr>
<tr>
<td>Late-onset sepsis</td>
<td>Vancomycin + aminoglycoside. Duration dependent on pathogen and site.</td>
<td>Alternatives to vancomycin may be considered based on local epidemiology and clinical presentation. Aminoglycoside based regimen preferred to cephalosporin given reduced risk of resistance. Consider cephalosporin if meningitis suspected. Consider a carbapenem if third-generation cephalosporin recently received. Consider amphotericin for fungal etiologies. Tailor therapy to pathogen. Consider discontinuation of therapy if pathogen not isolated.</td>
</tr>
</tbody>
</table>

Nonantimicrobial treatment strategies

- Recombinant G-CSF
- Recombinant G-MSF
- IVIG
- Prevention strategies
  - IAP
  - Fluconazole prophylaxis
  - BLF supplementation with a probiotic, Lactobacillus rhamnosus (GG)

BLF, bovine lactoferrin supplementation; EOS, early-onset sepsis; GBS, group B streptococcus; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IAP, intrapartum antimicrobial prophylaxis; IVIG, intravenous immunoglobulin; LGG, Lactobacillus rhamnosus GG; LOS, late-onset sepsis; NICUs, neonatal intensive care unit; RCTs, randomized, controlled trials; VLBW, very low birthweight.


gestational age may optimize antimicrobial utilization. Peak and trough measurements of antimicrobials may be useful to ensure therapeutic levels and minimize toxicity if the agent is administered for more than 2-3 days and is indicated for certain infections such as meningitis where CSF penetration and levels must be monitored. Trough measurements may be indicated in infants with compromised kidney or liver function who are receiving potentially nephrotoxic or hepatotoxic agents.

Treatment of newborn infants whose mothers received antibiotics during labor should be individualized. If early-onset sepsis is thought to be likely, treatment of the infant should continue until the infant remains asymptomatic for 24-72 hr and clinical and laboratory evidence of recovery is apparent. Furthermore, in the context of intrapartum antibiotic use, it is important to consider that the organism causing infection may be resistant to the intrapartum therapy, thus influencing selection of empiric antibiotics for the infant. For dosing regimens, see organism-specific chapters in Part XVII of this textbook.

DIRECTED THERAPY

Once the pathogen has been identified and its susceptibility determined, the most appropriate antimicrobial should be administered. For most Gram-negative enteric bacteria, ampicillin and an aminoglycoside or a third-generation cephalosporin (cefotaxime or ceftazidime if Pseudomonas coverage is needed) should be used. Enterococci should be treated with both a penicillin-containing antibiotic and an aminoglycoside, if the Enterococcus is susceptible to gentamicin. The addition of gentamicin to a penicillin provides synergistic bactericidal and postantibiotic effects. Ampicillin alone is adequate for L. monocytogenes, and penicillin suffices for GBS. Clindamycin or metronidazole is appropriate for anaerobic infections; metronidazole is preferred for anaerobic infections that involve the CNS because of its better CNS penetration, compared to clindamycin.

Third-generation cephalosporins, such as cefotaxime, are valuable additions for treating documented neonatal sepsis and meningitis because (1) the minimal inhibitory concentrations of these agents needed for treatment of Gram-negative enteric bacilli are much lower than those of the aminoglycosides, (2) excellent penetration into CSF occurs, and (3) relatively higher doses may be administered with less toxicity. The end result is much higher bactericidal titters in serum and CSF than is achievable with ampicillin-aminoglycoside combinations. However, the routine use of third-generation cephalosporins for suspected sepsis in neonates is not optimal without a clear indication for broader spectrum empiric therapy. Routine third-generation cephalosporin use has been linked to the rapid emergence of resistant organisms, Candida sepsis, and antibiotic-associated diarrhea in neonates.
ANTIMICROBIAL RESISTANCE
The emergence of antibiotic resistance among pathogens that infect newborns is of great concern. Vancomycin-resistant enterococci and vancomycin-insensitive S. aureus are emerging pathogens resulting from the widespread use of vancomycin. Although vancomycin use cannot be avoided in neonatal units where methicillin-resistant S. aureus is endemic, its use can be reduced by limiting empirical therapy to patients with a high suspicion of severe infection with coagulase-negative staphylococci (severely ill neonate with an indwelling intravascular catheter) and by discontinuing therapy after 2-3 days when blood culture results are negative. When susceptibility results are available and there is no evidence of CNS or endovascular involvement, clindamycin may be a suitable alternative for therapy of uncomplicated bacteremia and skin and soft tissue infections in a neonate.

BACTEREMIA
If a neonate’s condition permits, it is ideal to obtain a repeat blood culture from the site of the positive culture at the time of identification of the organism. This second culture may be helpful, especially in situations where the organism isolated would not be susceptible to the empiric or directed therapy that a neonate is receiving. Therapy for most bloodstream infections should be continued for a total of 7-10 days, or for at least 5-7 days after a clinical response has occurred. The duration of therapy is optimally calculated from the date of first negative culture. If successive blood cultures are notable for the presence of pathogens, the possibility of an infected indwelling catheter, endocarditis, an infected thrombus, an occult abscess, subtherapeutic antibiotic levels, or resistant organisms should be considered. A change in antibiotic, longer duration of therapy, or removal of the catheter may be indicated. Consultation with a pediatric infectious disease specialist may be indicated.

PNEUMONIA
A combination of ampicillin and an aminoglycoside or cefotaxime is appropriate for pneumonia that develops during the 1st 7-10 days of life. Nosocomial pneumonia, which generally manifests in the 2nd wk of life can be treated empirically with ampicillin or vancomycin and an aminoglycoside or a third-generation cephalosporin. Pseudomonas pneumonia should be treated with an agent to which the organism is susceptible. Some experts would consider the use of dual therapy for multidrug resistant organisms; however, the benefits of this therapy may vary based on host and pathogen. Pneumonia caused by C. trachomatis usually presents between the 1st and 3rd mo of life and is usually treated with oral erythromycin. The effectiveness of erythromycin in treating pneumonia caused by C. trachomatis is approximately 80%; in certain clinical situations, a second course of therapy might be required. Data are limited regarding the use of macrolides, such as azithromycin, for neonatal C. trachomatis pneumonia, although some practitioners prefer this agent to erythromycin because of the shorter course of azithromycin and the slightly increased risk of pyloric stenosis associated with oral erythromycin in neonates <6 wk of age. U. urealyticum infections may be treated with erythromycin.

MENINGITIS
Empiric antimicrobial therapy for bacterial meningitis should include ampicillin in doses used for meningitis, unless staphylococci are likely, in which case vancomycin may be considered. Neonates with shunts may be predisposed to developing meningitis and ventilcrititis attributable to resistant Gram-positive organisms. Cefotaxime or gentamicin in meningitic doses are appropriate choices for empiric Gram-negative coverage. Susceptibility testing of Gram-negative organisms is important because resistance to cephalosporins and aminoglycosides is common. Most aminoglycosides administered by parenteral routes do not achieve sufficiently high antibiotic levels in the lumbar CSF or ventricles to inhibit the growth of Gram-negative bacilli. Therefore, some experts recommend a combination of intravenous ampicillin and a third-generation cephalosporin for the treatment of neonatal Gram-negative meningitis. Cephalosporins should not be used as empirical monotherapy in neonates <3 mo of age when early or late onset lysterosis is suspected because L. monocytogenes is resistant to cephalosporins. Although a rare cause of meningitis in the neonate, enterococci are also resistant to cephalosporins.

Meningitis caused by GBS usually responds clinically within 24-48 hr of antimicrobial therapy. Therapy should be continued for 14-21 days. Gram-negative bacilli may continue to grow from repeated CSF samples for 72-96 hr after the initiation of effective therapy, as a result of the intracellular habitat of many organisms. Treatment of Gram-negative meningitis should be continued for 21 days or for at least 14 days after sterilization of the CSF, whichever is longer. P. acruina meningitis should be treated with ceftazidime or meropenem, assuming that the isolate is susceptible. Metronidazole is the treatment of choice for infection caused by B. fragilis and other anaerobic organisms. Prolonged antibiotic administration, with or without surgical drainage is indicated for neonatal cerebral abscesses. Imaging is recommended for patients with suspected ventriculitis, hydrocephalus, or cerebral abscess (initial and follow-up assessments) and for those with an unexpectedly complicated course (prolonged coma, focal neurologic deficits, persistent or recurrent fever).

Neonates with suspected neonatal herpes meningencephalitis should receive intravenous acyclovir; empirical antibacterial therapy may be considered in symptomatic infants with a CSF mononuclear pleocytosis, but this should be discontinued and acyclovir continued if bacterial cultures are negative and a CSF HSV PCR is positive. Supportive care is the current recommended management for severe enteroviral infections such as meningencephalitis, carditis, and hepatitis. There are currently no Food and Drug Administration-licensed therapies for neonatal enteroviral infections. The effectiveness of enterovirus immunoglobulin is unknown. A phase II double-blind, placebo-controlled virologic efficacy trial of pleconaril in neonatal enteroviral infections concluded enrollment in 2010 and data analysis is ongoing.

ADJUNCTIVE THERAPIES
Treatment of neonatal infections may be divided into antimicrobial therapy for the suspected or known pathogen and supportive care. Careful attention to respiratory and cardiovascular status is mandatory. Adequate oxygenation of tissues should be maintained; ventilatory support is frequently necessary for respiratory failure caused by sepsis, pneumonia, pulmonary hypertension, or acute respiratory distress syndrome. Refractory hypoxia and shock may require extracorporeal membrane oxygenation, which has reduced mortality rates in full-term infants with respiratory failure. Shock and metabolic acidosis should be identified and managed with fluid resuscitation and inotropic agents as needed. Corticosteroids should be administered only for adrenal insufficiency and in cases of TB meningitis. Fluids, electrolytes, and glucose levels should be monitored carefully with correction of hypovolemia, hyponatremia, hypocalcemia, and hypoglycemia/hyperglycemia. Hyperbilirubinemia should be monitored and treated aggressively with phototherapy and/or exchange transfusion, because the risk of kernicterus increases in the presence of sepsis and meningitis. Seizures should be treated with anticonvulsants. Parenteral nutrition is needed for any infant who cannot sustain enteral feeding.

DIC may complicate neonatal septicemia. Platelet counts, hemoglobin levels, and clotting times should be monitored. DIC is treated by management of the underlying infection, but if bleeding occurs, DIC management may require fresh-frozen plasma, platelet transfusions, or whole blood.

Because neutrophil storage pool depletion has been associated with a poor prognosis, therapies that increase the number or improve the quality of neutrophils have been studied, including granulocyte transfections, GM-CSF, and G-CSF. The use of G-CSF or GM-CSF abolishes sepsis-induced neutropenia, but none of these therapies has been shown to definitively improve survival.

It is important to remember that nonbacterial infectious agents can produce the syndrome of neonatal sepsis. HSV infection requires immediate specific treatment, as does systemic Candida infection. Treatment and other aspects of various nonbacterial infections are discussed in detail in other sections: TB (see Chapter 215), syphilis (see
Complications of bacteremic infections include endocarditis, septic emboli, abscess formation, septic joints with residual disability, and osteomyelitis and bone destruction. Recurrent bacteremia is rare (<5% of patients). Candidemia may lead to vasculitides, endocarditis, and endophthalmitis, as well as to abscesses in the kidneys, liver, lungs, and brain. Sequelae of sepsis may result from septic shock, DIC, or organ failure.

Mortality rates from the sepsis syndrome depend on the definition of sepsis. In adults, the mortality rate approaches 50%, and the rate in newborn infants is probably at least that high. Reported mortality rates in neonatal sepsis are as low as 10%, because all bacteremic infections are included in the definition. Several studies have documented that the sepsis case fatality rate is highest for Gram-negative and fungal infections.

The case fatality rate for neonatal bacterial meningitis is between 20% and 25%. Many of these patients have associated sepsis. Risk factors for death or for moderate or severe disability include seizure duration >72 hr, coma, need for inotropic agents, and leukopenia. Immediate complications of meningitis include ventriculitis, cerebritis, and brain abscess. Late complications of meningitis occur in 40-50% of survivors and include hearing loss, abnormal behavior, developmental delay, cerebral palsy, focal motor disability, seizure disorders, and hydrocephalus. Advanced imaging (CT, MRI) has demonstrated cerebritis, brain abscess, infarct, subdural effusions, cortical atrophy, and diffuse encephalomalacia in newborns surviving meningitis. A number of these sequelae may be encountered in infants with sepsis but without meningitis, as a result of cerebritis or septic shock. Extremely low birthweight infants (<1,000 g) with sepsis are at increased risk for poor neurodevelopmental and growth outcomes in early childhood.

MOTHERLATERAL STRATEGIES

Maternal immunization protects the mother against vaccine-preventable diseases that can cause intrauterine infections (rubella, hepatitis B, VZV) and may also protect the infant via passive transfer of protective maternal antibodies (tetanus). CMV vaccines are under study. Toxoplasmosis is preventable with appropriate diet and avoidance of exposure to aged cat feces. Malaria during pregnancy can be minimized with chemoprophylaxis and use of insecticide-treated bed nets. Congenital syphilis is preventable by timely diagnosis and appropriate early treatment of infected pregnant women.

Aggressive management of suspected maternal chorioamnionitis with antibiotic therapy during labor, along with rapid delivery of the infant, reduces the risk of early-onset neonatal sepsis. Vertical transmission of GBS and early-onset GBS disease is significantly reduced by selective intrapartum chemoprophylaxis (see Chapter 184). A number of candidate GBS vaccines are currently being studied. Neonatal infection with Chlamydia can be prevented by identification and treatment of infected pregnant women (see Chapter 226). Mother-to-child transmission of HIV is significantly reduced by maternal antiretroviral therapy during pregnancy, labor, and delivery, cesarean section delivery prior to rupture of membranes, and antiretroviral treatment of the infant after birth (see Chapter 276).

ANTIFUNGAL PROPHYLAXIS

Prophylactic administration of fluconazole during the 1st 6 wk of life reduces fungal colonization and invasive fungal infection in extremely low birth weight infants—those with birth weights <1000 g. In addition to the individual benefit afforded by prophylaxis for VLBW neonates, fluconazole prophylaxis may have a community impact by decreasing the overall fungal burden of a NICU. Results from more than 14 trials at multiple institutions with 3,100 neonates suggests that fluconazole prophylaxis decreases colonization of the urine, gastrointestinal tract, and integument, without promoting the development of resistance and without adverse effects. Based on an annual United States preterm birth cohort of approximately 30,000 VLBW infants, it has been estimated that fluconazole prophylaxis could prevent approximately 2,000-3,000 cases of invasive candidiasis, approximately 200-300 deaths, and the adverse neurodevelopmental outcomes of invasive candidiasis in approximately 400-500 infants per year. Differing baseline rates of fungal infections, practices related to central venous catheter removal, severity of illness, and practices related to the use of broad-spectrum antimicrobials make universal recommendations regarding prophylaxis challenging.

Neonatal practices that may reduce the risks of invasive candidiasis include, limited use of broad spectrum antimicrobials, use of an amnoglycoside instead of a cephalosporin for empiric therapy when meningitis or antimicrobial resistance is not suspected, limitation of postnatal steroid use in VLBW infants, early enteral feeding, and the establishment of the neonatal gut microbiome with human milk feeding.

OTHER STRATEGIES FOR PREVENTION OF HEALTHCARE-ASSOCIATED INFECTIONS

Because of the burden of disease, additional strategies including lactoferrin and probiotic supplementation and the administration of antistaphylococcal monocolonal antibodies have been explored as strategies to prevent HAIs. Although antistaphylococcal monocolonal antibodies have not proven to be of benefit, preliminary data suggest that bovine lactoferrin (BLF) supplementation alone and in combination with probiotics may reduce late onset sepsis. A prospective, multicenter, double-blind, randomized placebo-controlled trial in 11 tertiary care NICUs compared BLF alone or in combination with the probiotic Lactobacillus rhamnosus GG (LGG). Over a 9 mo period from 2007-2008, 472 VLBW neonates received placebo, LGG and BLF, or BLF only, daily from birth through 30 days of life or 45 days. Compared with placebo, BLF supplementation with and without LGG reduced the incidence of the first late-onset sepsis episode in VLBW neonates. Further studies of lactoferrin, with and without probiotics, to reduce risk of neonatal sepsis are indicated.

ANTIMICROBIAL STEWARDSHIP

Antimicrobial utilization practices in NICUs influence the types of microorganisms responsible for neonatal sepsis and their resistance patterns. The CDC has initiated a campaign to prevent antimicrobial resistance in healthcare settings. This effort is designed to increase clinician awareness and to improve diagnosis and appropriate treatment of infection. The campaign supports involving infectious disease and pharmacy consultants, treating infections with an antimicrobial with the narrowest spectrum and discontinuing therapy when adequate therapy has been administered. Prevention of infections through optimizing infection control and enhanced surveillance are additional components of the campaign.

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